



# A pilot protocol and review of triple neuroprotection with targeted hypothermia, controlled induced hypertension, and barbiturate infusion during emergency carotid endarterectomy for acute stroke after failed tPA or beyond 24-hour window of opportunity

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**Abstract:** An alternative to tissue plasminogen activator (tPA) failure has been a daunting challenge in ischemic stroke management. As tPA is time-dependent, delays can occur in definitive treatment while passively waiting to observe a clinical response to intravenous thrombolysis. Until today, uncertainty exists in the management strategy of wake-up stroke patients or those presenting beyond the therapeutic tPA window. Clinical dilemmas in these situations can prolong the transitional period of inertia, resulting in an adverse neurological outcome. We propose and review an innovative approach called triple neuro-protection (TNP), which encompasses three technical domains-targeted hypothermia, systemic induced hypertension, and barbiturates infusion, to protect the brain during carotid endarterectomy after failed tPA and/or beyond the 24-hour therapeutic mechanical thrombectomy window. This proposal assimilates discussion on the clinical evidence of the individual domains of TNP with our own clinical experience with TNP. Our first TNP was successfully employed in a 55-year-old man in 2015 while performing emergency carotid endarterectomy after he was referred to us 72 hours post tPA failure. The patient had a successful clinical outcome despite being in therapeutic inertia with 90–99% ipsilateral carotid stenosis and contralateral occlusion on presentation. In the last five years, we have safely used TNP in 25 selected cases with favourable clinical outcomes.

**Keywords:** Triple neuroprotection; therapeutic hypothermia; induced hypertension; barbiturates; stroke; ischemia; review

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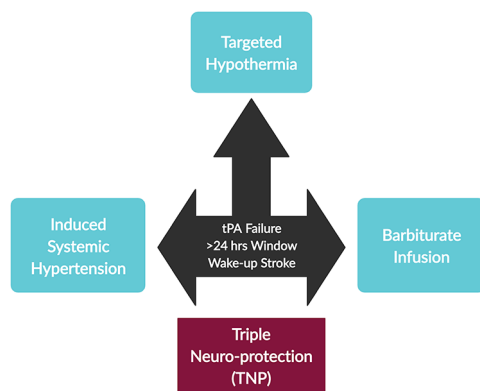
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## Introduction

Tissue plasminogen activator (tPA) is an established therapy for acute stroke, but its success and therapeutic range is limited. However, therapeutic alternatives to tPA have been a daunting question in ischemic stroke management. The

addition of mechanical thrombectomy is well established in patients with internal carotid artery (ICA), or proximal middle cerebral artery (M1), occlusion, as demonstrated by studies including Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) (1), Solitaire™ With the



**Figure 1** Three components of triple neuro-protection: targeted hypothermia, induced systemic hypertension, and barbiturate infusion.

Intention For Thrombectomy as PRIMARY Endovascular Treatment (SWIFT PRIME) (2), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) (3), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) (4), Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) (5) and Mechanical Thrombectomy After Intravenous Alteplase Versus Alteplase Alone After Stroke (THRACE) (6). However, not all patients show clinical improvement following thrombectomy (7), and the outcome after thrombectomy declines with more extended latent periods from symptoms to arterial puncture (8,9). Time is Brain (10), and each one-hour delay in reperfusion is invariably associated with worsening disability. Clinical dilemmas in these situations can compromise the neurological outcome. To overcome these practical challenges, we propose an innovative alternative approach in patients undergoing emergency carotid endarterectomy (CEA) after failed tPA and/or beyond the 24-hour therapeutic mechanical thrombectomy window.

### Triple neuroprotection (TNP)

TNP is a technique employed to protect the brain through targeted hypothermia, systemic induced hypertension, and barbiturates infusion (*Figure 1*). Decreased perfusion

in a specific cerebral region will result in an initial loss of function. Nevertheless, the loss of function is potentially reversible if immediate intervention is provided. These hypoxic areas of brain tissue, coined as ‘ischemic penumbra’ by Astrup *et al.* (11), are dynamic in nature and provide us with an opportunity to act swiftly before the onset of irreversible brain damage (12,13).

### Mechanism of action

Based on the proposed three critical components of the TNP (targeted hypothermia, systemic induced hypertension, and barbiturate infusion), it is postulated that the composite benefit will be synergistic in comparison to the independent components. Targeted hypothermia preserves the ischemic brain section by restricting the penumbral tissue recruitment into the ischemic core. Limitation of the penumbra is achieved by vasoconstriction and subsequent reduction in cerebral edema (14). Maintenance of the blood-brain barrier (BBB) decreases free radical formation, undoubtedly leading to a slowdown of the inflammatory cascade, cell apoptosis, and caspase activation (15). Brain cells will better adapt to the ischemic insult and ATP reduction, with a resultant curtailment in the cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>). Noteworthy, at least 50% CMRO<sub>2</sub> is required for visible neuro-protection. However, induced hypothermia (34 °C) cannot achieve this specific target alone and lowers CMRO<sub>2</sub> by 20% only (16). Therefore, barbiturate infusion can be safely employed to supplement the reduction in CMRO<sub>2</sub>, as it is capable of further lowering the CMRO<sub>2</sub> beyond 50%. Finally, induced systolic hypertension, when combined with targeted hypothermia and barbiturate infusion, maintains cerebral perfusion via retrograde carotid flow and an increase in stump pressure. This combination of targeted hypothermia, systemic induced hypertension, and barbiturate infusion during relative cerebral ischemia work together to decrease the demand (low cerebral metabolism and energy consumption) and increase the supply (cerebral blood flow) to maintain the ischemic tissue integrity.

### Evidence to support individual components of TNP

#### Targeted hypothermia

Therapeutic hypothermia is a technique of achieving core body temperature between 32 and 34 °C for medical purposes (15). Brain injury is expected to raise the brain’s

temperature more than the core body temperature (17). Many studies associate increased body temperature with unfavorable outcomes (18,19). Hypothermia in acute ischemic stroke was mainly achieved in the past to manage malignant brain edema (18). However, the utility of hypothermia has been extended in recent times in ischemia-reperfusion injury during thrombolysis or mechanical thrombectomy (20).

Targeted therapeutic hypothermia lowers lactate and pyruvate concentrations (16,21). It is capable of decreasing the excitotoxic neurotransmitter glutamate discharge, which results in free radical decrement but accentuates glucose usage by ischemic tissues (22). It also inhibits cellular Ca<sup>2+</sup> influx and reduces peri-infarct depolarization (23). This constellation of active cellular mechanisms suppresses BBB disruption and decreases edema, thereby, maintaining cerebral autoregulation to reduce post-ischemic hypo or hyperperfusion (24,25). Finally, targeted hypothermia is also believed to modify ischemia associated gene expression (26).

Therapeutic or induced hypothermia has been effective in ischemia-reperfusion injury and cerebral edema. Rapid cooling has been shown to enhance the neurological outcome and overall survival following cardiocirculatory arrest (27,28). Cooling should be maintained as early as possible, preferably within 72 hours before the irreversible tissue damage has initiated (19,29). Although there is a scarcity of focused studies relating to therapeutic hypothermia in ischemic brain injury, its utility has already been established post-cardiac arrest (30-33). A lower metabolic rate will progressively improve global neurological outcomes and reperfusion injury (34). Early cooling has been used in a phase II trial with stroke patients to establish its safety and feasibility (35). Induced therapeutic hypothermia for 1 to 3 days has shown to be effective in dense stroke patients treated without neuro-vascular intervention (15,30,31). COOL AID (36), is the only existing study that employed targeted hypothermia (32 °C) in acute ischemic patients during thrombolysis. Targeted hypothermia proved safe, with the explicit exception of a minor non-critical temporary sinus bradycardia. This study established targeted hypothermia following thrombolysis as a feasible option for neuroprotection in acute stroke.

### ***Controlled induced hypertension***

Perioperative stroke and/or cognitive dysfunction are an established operative risk of CEA, which have been attributed to micro embolism or relative ischemia due to

reduced collateral blood supply during carotid artery cross-clamping (37-40). Early cognitive dysfunction, evident 24 hours post-surgery, is more prevalent than stroke (25% vs. 5%) (41,42) and results from reduced cerebral blood flow (43,44). To prevent these complications, mean arterial pressure (MAP) is usually kept around 20% higher than the baseline to maintain collateral blood flow and sustain cerebral perfusion (45-48). Heyer *et al.* (49) have shown a low risk of early cognitive dysfunction even with MAP  $\geq 20\%$  of the baseline while cross-clamping of the carotid artery.

Cerebral collateral perfusion pressure (CCPP) plays an essential role in avoiding perioperative ischemia. LeSar *et al.* (50) have already demonstrated the benefit of maintaining permissive hypertension with a significant reduction of operative duration and need for shunting in both awake and sedated patients. Shunting can be avoided in more than two-thirds of the cases, as there are conflicting views and evidence regarding the usefulness of shunting (51). Avoidance can reduce subsequent hazards of the procedure, which can include embolization, occlusion, or increased operative time (52,53). For this reason, we avoided shunting in all our patients.

As maintenance of CCPP is vital to reduce perioperative ischemia, adequate CCPP without the employment of shunts can be made possible with an increment of MAP. Systolic blood pressure maintained between 180–200 mmHg during carotid clamping decreases ischemic stroke risk by increasing collateral blood flow and tissue perfusion across carotid stenosis (49). In TNP, we employ induced systemic hypertension to maintain cerebral perfusion by increasing the retrograde carotid flow and stump pressure in combination with hypothermia and barbiturate infusion.

### ***Barbiturate infusion***

Adequate cerebral blood flow promotes neuronal survival based on the classical supply and demand theory—*‘the higher the cerebral metabolism, the greater the required blood flow.’* Decreasing cerebral metabolic demand will not only require less blood flow but also protects the brain during relative ischemia. There have been many experiments in the past to produce these neuroprotective effects. Barbiturates are the first pharmacological agent to show this favorable metabolic brain effect (54). Barbiturates slow neurotransmission and increase brain adaptability to ischemia (55). Michenfelder *et al.* (56-58) showed the barbiturate induced dose-dependent decrement in the brain’s metabolic activity in the

animal model, with a sequential abatement in EEG activity and ATP depletion. As energy required to produce electrical activity in the brain can be channeled to the surrounding neurons for fulfilling their basal metabolic needs, neuronal energy expenditure is reduced up to half with an isoelectric EEG pattern.

Thiopental was the first to be tried for perioperative neuro-protection (55,59-61). Nussmeier *et al.* (60) proved 'first-in-humans' cerebral neuroprotection by administering thiopental in a prospective study conducted to assess the neuropsychiatric effect of the barbiturate during cardiopulmonary bypass. In cardiac surgery, barbiturates induce cerebral protection during hypothermic circulatory arrest (62). They have displayed beneficial cerebral effects while performing CEA without adverse cardiovascular outcomes (63,64). They reduce oxygen demand throughout relative tissue ischemia induced by arterial clamping (65,66). Thiopentone has also been demonstrated to provide cerebral protection during CEA and intracranial aneurysm clipping (67). During carotid clamping, Gross *et al.* (68) used thiopental-induced EEG burst suppression in hypertension unresponsive ischemia, carefully replacing it with technically challenging and dangerous in-line arterial shunting. Young *et al.* (69) also showed a survival benefit of the prophylactic barbiturate and therapeutic hypothermia in asphyxia.

Although barbiturates have convincingly been shown to maintain arterial, cardiovascular, and cerebral blood flow during focal ischemia, there are many conflicting reports in global ischemia (56,70). Neuroprotection with the barbiturate might not be reproducible with a complete loss of cerebral blood supply. Specifically, it may not be possible to extend these beneficial effects in a condition of total ischemia when the EEG becomes isoelectric within 90 seconds of complete cessation of cerebral blood supply. After that, further depression of EEG activity is neither possible nor relevant (61,71). Nevertheless, during incomplete ischemia as in most unilateral carotid stenosis complicated with tPA failure, this neuroprotective effect can have a significant impact on the patient perioperative survival, and it can be combined effectively with hypothermia and induced systemic hypertension.

### Our experience with TNP

We undertook our first TNP case in 2015 while performing emergency CEA in a 55-year-old man who was referred to us 72 hours after failed tPA. He was in therapeutic

inertia despite a 90–99% ipsilateral carotid stenosis and contralateral occlusion. On presentation, his Rankin and ABCD3-I scores were 4 and 12, respectively. We had two choices, either act or wait. After a thorough discussion with all the concerned stakeholders, including the patient, his family, and surgical staff, we decided to act and explore the possible therapeutic options—emergency CEA with TNP. The patient and his family members were counselled regarding the risk of the procedure and sequelae of the hyper-perfusion syndrome. Consent was obtained, and risk reduction possibilities were carefully discussed with our anesthetic colleagues. All our cases were performed under general anaesthesia because it was not feasible to undertake TNP using local anaesthesia. First, systolic hypertension (200 mmHg) was induced, and brain activity suppressed to an iso-electric point with IV barbiturates. After that, a pediatric bronchial suction catheter was used to retrieve thrombus from A1, M1. We did not use a carotid shunt to avoid internal carotid artery embolic dislodgement. Following 24 hours of intubation, the patient was capable of full mobility and self-care, and his Rankin score reverted to 0. This successful outcome impelled us to apply the triple neuroprotective mechanism in selected patients, whom we previously would have denied surgical interventions after failed tPA or beyond the 24-hour window of opportunity.

It is our usual practice to give a dose of 75 mg of clopidogrel on the evening before surgery in the elective setting. However, in these emergency cases, the surgery took place within hours; therefore, clopidogrel was not given pre-operatively. We did not give high-dose statins because of the associated risk of intracranial hemorrhage, especially in the context of intravenous tPA administration (72,73). Heparin is given intra-operatively (80 IU/kg) before clamping, and this is reversed at the end of surgery with protamine (74). In line with the European Society of Vascular Surgery (ESVS) guidelines, antiplatelet therapy is maintained for the long-term.

Since this first case, we have employed TNP in 25 patients while performing emergency CEA, amongst 12,000 patients referred to us with carotid artery disease between 2015 and 2019 (75). The relatively low procedure count is due to the reservation of the technique for specific patients only, i.e., those who have either failed tPA or those who have passed the recommended time for acute stroke intervention. More than 95% of the selected cases had 80–99% stenosis on the ipsilateral side. Following the procedure, there were no incidents of peri-procedural complications, like bleeding, cranial nerve injury, myocardial infarction, or

death. Twenty-two patients (88%) were discharged home after a mean hospital stay of 8.4 days while the remaining 3 (12%) needed long term rehabilitation. Noteworthy, all the patients remained asymptomatic after the first year of follow up.

## Discussion

Mechanical thrombectomy offers a favorable outcome in ischemic stroke patients. However, mechanical thrombectomy in patients with concomitant proximal severe carotid artery disease is time-dependent, and success wanes with therapeutic delay. The possible delay could result from clinical dilemmas after tPA failure, uncertainty about optimal management of proximal internal carotid artery/common carotid artery disease, and crossing of the 24-hour therapeutic window. Although thrombectomy can be extended up to 24 hours, as per DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) (76) and The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) (77) trials, the patient selection remains challenging. For these subgroups of patients, TNP is an innovative technique that employs synergistic utility of credible, evidence-based pragmatic approaches.

TNP can also be a viable option in wake-up stroke (WUS) patients, where patients wake up with stroke after going for routine sleep. WUS patients constitute approximately 15–30% of ischemic stroke patients (78-80). It is not possible to clinically pinpoint the exact timing of stroke onset in WUS, leaving clinicians with a therapeutic dilemma (81,82). Unfortunately, there is insufficient evidence for treatment recommendations in these patients, and they are particularly vulnerable to a disability or even death. TNP in these subgroups serves a dual purpose—(I) overcome therapeutic uncertainty, and (II) increase favorable outcomes.

During emergency CEA, surgeons tend to avoid shunts to eliminate the risk of distal embolic dislodgement. At this point, there is a need for an innovative approach to global neural protection resulting from ischemia. Induced therapeutic hypothermia remains a core component of TNP. Cooling during brain surgeries has already proven to be safe and feasible. Targeted therapeutic hypothermia is achieved in a controlled environment and is clinically safe. A Cochrane review by Galvin *et al.* (83) did not demonstrate any potential harm of induced hypothermia in complex neurosurgery. Targeted hypothermia is already proven in

stroke patients. Den Hertog *et al.* (84) showed a clinically meaningful effect of hypothermia in stroke outcomes. Brain hypothermia can also abate convulsions clinically (85-90). Cold saline has been used to terminate spontaneous electrical and stimulation-evoked brain discharges (91-93). Cooling of the brain has been traditionally achieved either with or without direct brain exposure under sedation or general anesthesia (85,94-96). In a pilot study, Bagić *et al.* (97) proved the safety of head-neck cooling in awake patients in refractory seizures. In traumatic brain injury, D'Ambrosio *et al.* (98) and Atkins *et al.* (99) also showed post-traumatic hypothermia as a viable therapeutic option for seizure reduction. Although all these studies were performed without neurovascular intervention, their safety can be extrapolated to TNP.

Shivering is the most established side effects during induced hypothermia, which can be effectively tackled with anticipation, rewarming therapy (or counter-rewarming), and benzodiazepines (100). About one-half of the patients are likely to suffer from a chest infection, depending on the extent of hypothermia (14). Chest infection risk can be decreased with intubation and mechanical ventilation (101). Although not common, prolonged hypothermia and slow controlled rewarming can also induce cardiac rhythm abnormalities, electrolyte disturbances, and hypoglycemia (63,102). We did not have any of these complications in our patients.

Conventional mechanical thrombus retrieval devices, like MERCI retriever (Stryker, Kalamazoo, MI), the Penumbra system (Penumbra, Alameda, CA), and Solitaire AB (Medtronic, Minneapolis, MN) compliment management of acute ischemic patients (103). MERCI retriever devices can be deployed for restoring blood flow in ischemic stroke patients regardless of tPA status (104). The Penumbra system helps in revascularization in large vessel intracranial occlusion (105). The Solitaire AB device, a self-expanding fully retrieval stent, is capable of trapping the clot within the stent matrix. Solitaire AB devices have been proven to have superior outcomes than the MERCI system (106). Recently, mechanical thrombectomy using ADAPT (A Direct Aspiration, First Pass Technique for the Endovascular Treatment of Stroke) has been increasingly used in many vascular institutions (107). A meta-analysis by Phan *et al.* (108) showed the superiority of ADAPT in comparison to the stent-retriever thrombectomy in terms of complete revascularization and expedited groin to reperfusion time, but without any discernible differences in the clinical outcome. Theoretically, mechanical removal

of an occluding large vessel thrombus represents the best management strategy (109), but practical limitations persist due to the relative suction sizes and subsequent risk of dislodgement. We employed pediatric bronchial suction (for size advantage) to retrieve thrombus from A1, M1, with a favorable outcome in TNP.

Stroke is the most significant complication in patients undergoing emergency CEA (110,111). Stroke rate can increase based on a multitude of factors, like tangential internal carotid clamping and accidental distal emboli migration to the brain. In our experiences with TNP, we encountered no such complications. We can state with confidence that decreasing the brain metabolic activity by TNP during the hypo-perfused state has reduced the risk of peri-procedural stroke. We only had one diabetic patient amongst the 25 emergency CEAs under TNP. Unfortunately, this diabetic patient suffered from hyperperfusion syndrome but was managed accordingly without any adverse outcome. Although it is relatively premature to infer conclusions based on only one case, we recommend being cautious when operating on people with diabetes as delayed stroke intervention could pose an added risk.

### Limitations

We acknowledge that TNP is still in the early phase and has several functional limitations. There are no controlled comparative studies to objectively compare and back up our claim about patient safety or potential efficacy. Our study was limited in the sample as a sufficiently large sample size for higher statistical power was not feasible in a single-center neuro intervention surgical unit. Trials are further limited by specific patient inclusion criteria, medico-legal background, and financial constraints. A prospective multicenter patient registry could be a good choice to report the clinical outcomes. Finally, we understand that the therapeutic benefit seen by us in the last 5 years with TNP cannot be solely attributed to TNP, and a multitude of factors may have contributed to the positive outcomes. For example, the concomitant use of pediatric suction after inducing systolic hypertension for flow reversal could have avoided denuding endothelium by retrieval devices, adding to the safety of this procedure. However, the overwhelming results and absence of visible adverse outcomes in patients who were in therapeutic inertia were encouraging for TNP. Therefore, although there is only preliminary evidence behind the TNP and we do not have Level I Evidence in

the form of a randomized controlled trial, we advocate TNP in challenging scenarios—where ‘no action’ is associated with high disability, and increased morbidity and mortality.

### Conclusions

TNP is a systematic approach consisting of three core components: targeted hypothermia, systemic induced hypertension, and barbiturate infusion and could be a viable option to aid emergency CEA in ischemic stroke patients, specifically for those where tPA has failed and/or the 24-hour therapeutic time window have elapsed. We safely employed TNP in 25 cases during the last 5 years with clinical success. Although our experience suggests TNP as a safe and effective routine therapeutic choice, we advocate for a more extensive controlled comparative study to establish its efficacy and safety.

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