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REVIEW

Targeted temperature management in neurological intensive care unit

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Abstract

Targeted temperature management (TTM) shows the most promising neuroprotective therapy against hypoxic/ischemic encephalopathy (HIE). In addition, TTM is also useful for treatment of elevated intracranial pressure (ICP). HIE and elevated ICP are common catastrophic conditions in patients admitted in Neurologic intensive care unit (ICU). The most common cause of HIE is cardiac arrest. Randomized control trials demonstrate clinical benefits of TTM in patients with post-cardiac arrest. Although clinical benefit of ICP control by TTM in some specific critical condition, for an example in traumatic brain injury, is still controversial, efficacy of ICP control by TTM is confirmed by both *in vivo* and *in vitro* studies. Several methods of TTM have been reported in the literature. TTM can apply to various clinical conditions associated with hypoxic/ischemic brain injury and elevated ICP in Neurologic ICU.

Key words: Targeted temperature management; Neuroprotective therapy; Ischemic/hypoxic encephalopathy; Intracranial pressure; Surface cooling; Endovascular cooling

Core tip: Two main purposes of targeted temperature management (TTM) in patients admitted in neurological intensive care unit are neuroprotective therapy and intracranial pressure (ICP) control. TTM is the most potent neuroprotective treatment due to its numerous methods of protection against ischemic/hypoxic injury. TTM provides capable ICP reductive action. Two most popular methods using in clinical practice and clinical trials are invasive endovascular technique and non-invasive surface cooling. Fast induction, smooth maintenance and slow rewarming are the important steps to achieve ideal TTM.

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INTRODUCTION

Clinical benefit of therapeutic hypothermia in patients with post-cardiac arrest syndrome (PCAS) has been demonstrated by two randomized control trials since 2002[1,2]. However, the term "therapeutic hypothermia" has been replaced with "targeted temperature management (TTM)" since 2011 after the meeting of five major professional physician societies[3]. TTM defines as a type of treatment that reduces a subject's core temperature until a specific target with the purpose in salvage or alleviate the tissue injury from deficiency of blood perfusion[4]. TTM is recognized as a only established neuroprotective therapy for hypoxic/ischemic brain injury, particularly in patients after cardiac arrest[5]. The clinical practice guidelines state that TTM should apply as a major treatment for patients following successful resuscitation from cardiac arrest[6-10].

Elevated intracranial pressure (ICP) is one of the common conditions found in patients admitted in neurologic intensive care unit (ICU)[11]. Many clinical and animal trials demonstrate that TTM effectively lowers ICP[12]. However, the application of TTM as ICP control in each particular disease, for examples in primary intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI) and cerebral infarct, needs to be proved by large randomized controlled trial[13].

HYPOXIC/ISCHEMIC CASCADE

Hypoxic/ischemic brain damage is associated with the abruption of cerebral blood flow (CBF)[14]. Cessation of brain circulation leads to compound neurologic damages, the so-called hypoxic/ischemic cascade[15]. After the deficiency of oxygen and circulation supplying occur, adenosine triphosphate (ATP) manufacturing malfunction develops[16]. Neurons and glials change from aerobic to anaerobic process, resulting in accumulation of lactic acids[17]. Cells become depolarized due to the sodium-potassium ATPase pumps failure, letting ions, particularly calcium (Ca^{2+}), to invade themselves[18]. Elevated intracellular Ca^{2+} stimulates the release of the well-known excitatory amino acid neurotransmitter such as glutamate[19]. Glutamate permits further Ca^{2+} influx the cells by activate the opening of Calcium-permeable NMDA receptors and AMPA receptors[20]. After excessive calcium Ca^{2+} influx, the production of deleterious substances including various free radicals, reactive oxygen species, phospholipases, ATPases, and endonucleases, the so-called excitotoxicity materials, initiates[21]. Membrane and mitochondria break down and lead to development of necrotic cells and apoptosis. Glutamate and other harmful materials are then released from these necrotic cells into the environment[22]. These materials cause further damage to adjacent cells. This continuous injury, the so-called reperfusion damage, usually starts when the cerebral tissue gets reperfused[23]. Inflammatory scavengers get accumulated to eat up the debris tissue and then generate many cytokines[24]. These toxic materials disrupt the blood-brain barrier (BBB). Destroyed BBB conducts to leakage of huge protein molecules particularly albumins into the environment causing brain edema[25]. Brain edema produces pressure effect of and further harm to adjacent brain tissue[26]. The hypoxic/ischemic cascade are shown in Figure 1.

ICP

The theory of ICP, the so-called Monro-Kellie doctrine, was first postulated by Alexander Monro in 1783 before George Kellie published the article support Monro's idea in 1824[27,28]. This theory states that since the skull is a permanent volume and the brain is enclosed by rigid meninges, therefore, alterations in the volume of the intracranial components will affect ICP[29]. The intracranial components include blood, cerebrospinal fluid (CSF), and brain tissue, all of which are relatively constant. An enlargement in one component or development of a mass lesion will elevate ICP and require a diminishing in another component in order to preserve the permanent intracranial volume[30]. An expanding lesion can initially shift CSF and blood out of the cranium without much change in ICP. However, this capacity to compensate for changes in volume has limitation. If the lesion continues expansion, ICP will get elevated[31]. Elevated ICP leads to cerebral herniation[32]. Moreover, increased ICP harms CBF by depressed cerebral perfusion pressure (CPP), where CPP is calculated by subtraction of ICP from mean arterial pressure[33].

MECHANISMS OF TTM

The multiple sites of actions are thought to be the protective effects of TTM on ischemic cascade[34]. These multiple sites of actions include prevention of BBB disruption, reduction of oxygen derivative free radical release, reduction of excitotoxic neurotransmitter production, anti-inflammatory action and delayed apoptosis[35]. The major neuroprotective effect of TTM in patients after cardiac arrest with restored of systemic circulation (ROSC) is apparently the protective effect on reperfusion damage[36]. Numerous effects resulted from reperfusion damage, including oxygen free radical production, excitotoxic neurotransmitter release, and calcium influx, are all diminished by TTM[5,6,34]. Moreover, TTM also reduces cerebral metabolic rate, protects mitochondrial break down and prevents cell membrane leakage[37,38]. The neurons and glials are finally prevented to turn apoptosis[38]. Protection of BBB damage is an important action of TTM[39]. Diminution of BBB disruption helps to

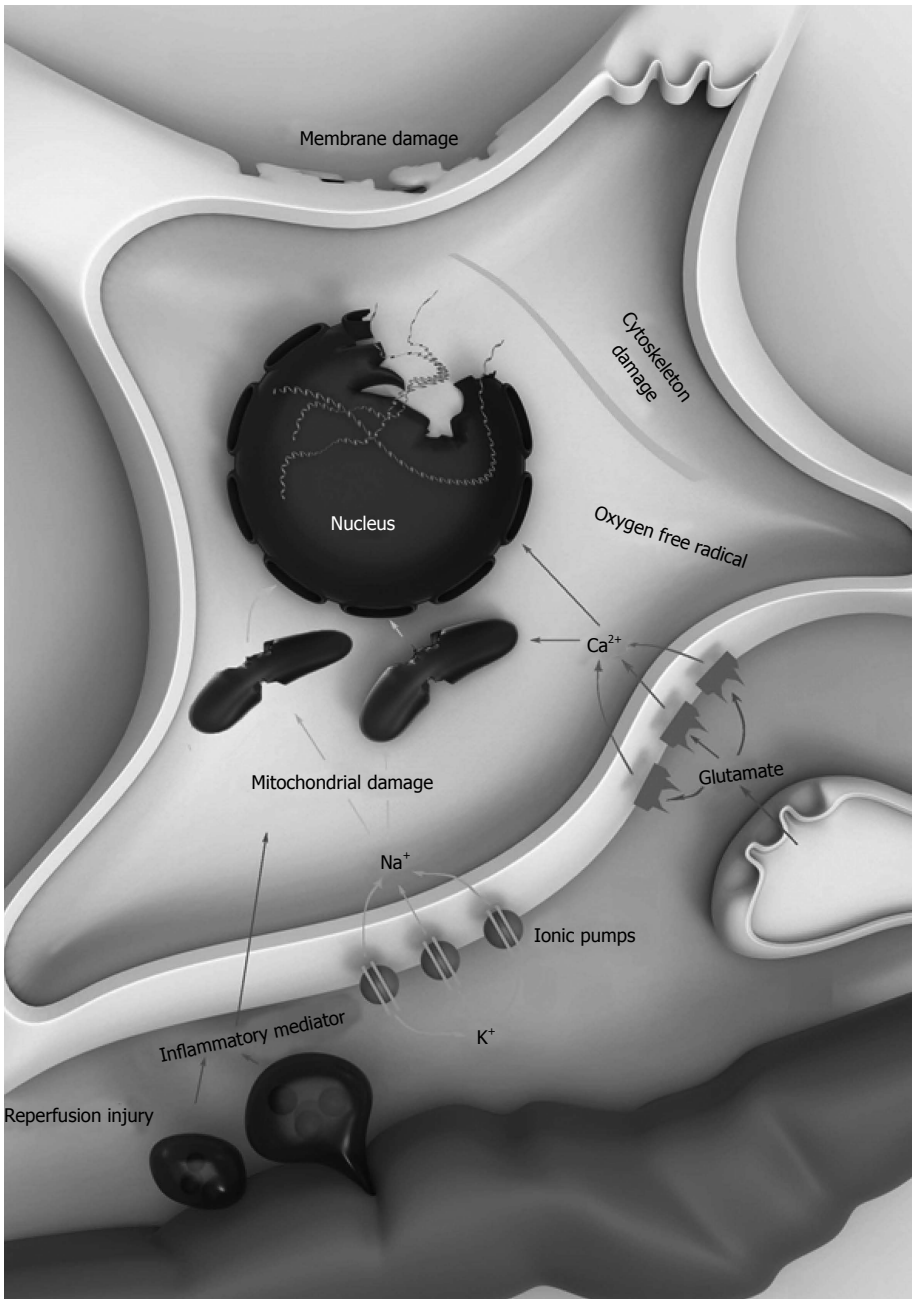

Figure 1 Hypoxic/ischemic cascade[44] (modified from ref. [44], use with permission).

reduce brain edema then lower ICP[38]. Effectiveness of ICP reduction by TTM in various brain disorders has been demonstrated in many clinical and experimental studies[12,40-43]. However, absolute profit of ICP control by TTM in diverse clinical features needs to be confirmed with large scale RCTs[3,13].

THE IDEAL TTM

The course of TTM is divided into three phases[44]. The beginning of TTM is known as induction phase. The main idea of induction phase is to lower the current core temperature to the target as fast as possible[45,46]. Subsequently, that target temperature is smoothly maintained for certain duration (usually for 24 h), the so-called maintenance or sustainment phase[45,46]. The last part, the so-called rewarming phase, the core temperature is slowly raised to the ordinary point with actively control rate, usually at 0.2-0.5 ℃/h[45,46]. Most of the important complications, particularly infection, usually happen during this last phase when the temperature is passively rewarmed with too rapid and out-of-control rate[4]. The ideal temperature curve of a patient with cardiac arrest treated with TTM is showed in Figure 2.

METHODS TO ACHIEVE IDEAL TTM

Many methods of TTM have been reported in the literature. Some methods are no longer utilized in

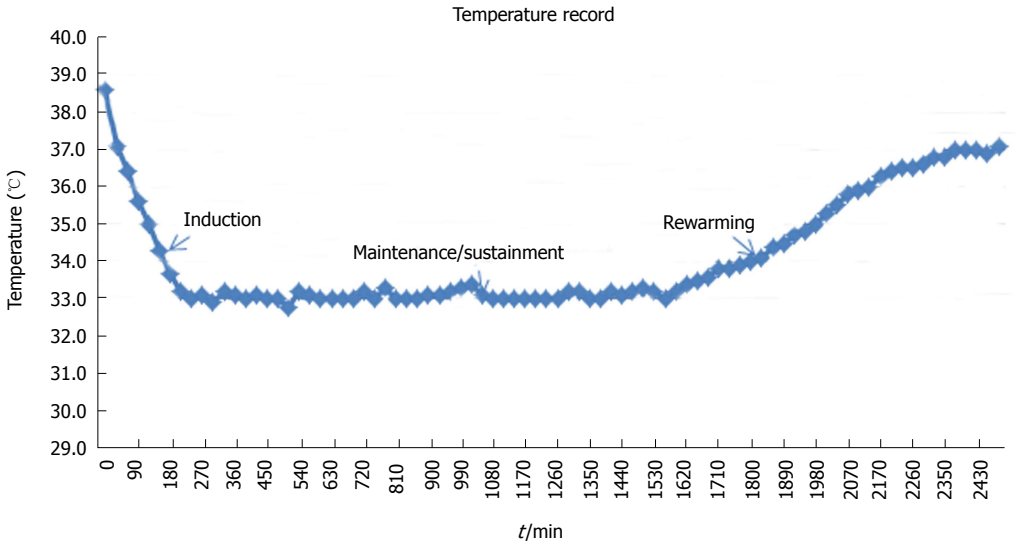

Figure 2 Temperature record of a patient with post-cardiac arrest with targeted temperature management.

clinical practice any more due to their unfeasibility or their ineffectiveness. The method with antipyretic drugs alone are, of course, not sufficient to achieve ideal TTM[47]. Under lack of electricity source circumstance, intravenous cold crystalloid solution may be helpful for initiation of TTM during pre-hospital period[48,49]. However, large volume is needed for induction phase. It is still not possible to achieve ideal TTM with intravenous cool fluid alone. Cooling helmets or hoods is effective to achieve selective cerebral TTM in infants however it seems to be ineffective in adults[6,50]. The two most accepted methods in clinical practice and major clinical trials are non-invasive surface technique and invasive endovascular technique[51,52].

Invasive endovascular methods

The hallmark of invasive endovascular techniques is central venous catheter with extracorporeal cooling machine[4]. The central venous catheter can be sticked *via* femoral, jugular or subclavian vein. Of course, the auto-feedback temperature regulated system is integrated with the machine. Two commercial brands are obtainable in universal market: CoolGard 3000® and Celcius Control System®. The advantage of endovascular system is effective performance including rapid temperature reduction to the target, smoothly sustainment of target temperature and rewarm with actively controlled rate[53,54]. Application of non-pharmacologic shivering control with skin counter-warming is much convenient and more effective during endovascular cooling[55]. Without sedative effect from pharmacologic shivering control, intubation for airway protection can be avoided under skin counter-warming[56]. That's why endovascular method is the recommend technique in several studies of TTM in subjects with acute ischemic stroke[57-59]. However, catheter-related complications and limitation of central venous access are disadvantage issues for endovascular method[51,60].

Non-invasive surface methods

Compression of ice packs to neck, axilla and groin is the simplest way for surface cooling. Two landmark randomized-controlled-trials (RCT) for TTM in patients with PCAS demonstrated effectiveness of this ice packs application[1,2]. However, disadvantage of this technique is awkward, required strenuous staff effort, unreliable temperature control and high risk for complications[61]. The auto-feedback temperature regulated machine provides reliable temperature management and is favorable to perform in clinical practice[47]. The machine comes with circulatory cold water blankets/pads or cold air-flow blankets. Several trademarks of machine are commercially distributed in the worldwide market, including ArcticSun®, CritiCool® andBlanketrol®. The effective automatic cooling system with temperature feedback of the machine helps rapidly lower the temperature to the target and supports slowly rewarm back to the normal baseline temperature. Core temperature monitoring straight connected to the machine is the key for auto-feedback temperature regulated system. The temperature of water within the blankets or pads is automatically regulated by the machine upon target temperature setting and feedback data from core temperature measurement[52]. The surface method with cold water pads is showed in Figure 3.

EMCOOL® pads consist of graphite elements, the high heat conductivity, for cooling media which apply right to the superficial skin. This pads have to get frozen up in ordinary freezer to become 9 ℃ before application however do not require power supply while using[62]. Consequently, this system is extremely practical in pre-hospital situation for TTM induction[63].

The novel esophageal cooling device, the most recent non-invasive method, shows preliminary benefit

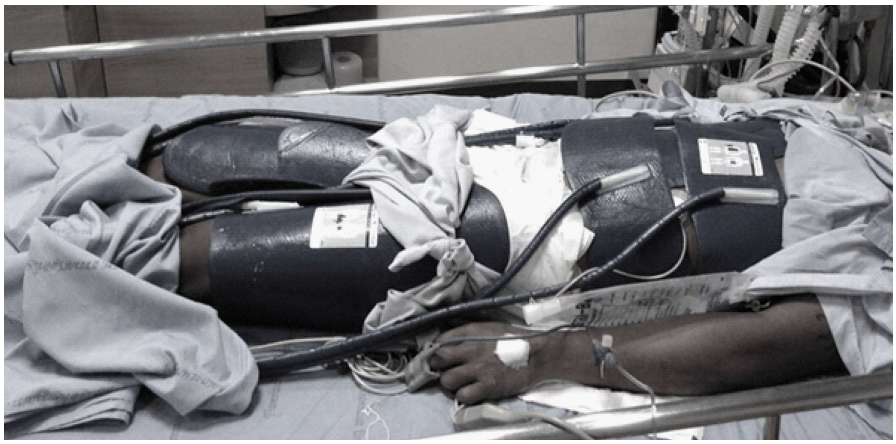

Figure 3 A patient is undergoing targeted temperature management with cold water pads.

of its use in PCAS patients[64]. The United States Food and Drug Administration has already approved this device[65].

SHIVERING AND COMMON PHYSIOLOGIC RESPONSE

Peripheral vasoconstriction is the initial physiologic response when temperature begins to go down[66]. When temperature declines to the certain point, shivering usually occurs[4]. Occurrence of shivering may represent intact physiologic response and indicate good neurologic outcomes[67]. Wonderful shivering control is a key of success to achieve ideal TTM and should be included in the treatment protocol[55,68]. Shivering is usually monitored with the Bedside Shivering Assessment Score during TTM (Table 1)[69]. Elevated peripheral vascular resistance during induction phase of TTM is usually transient and takes no effect to systemic blood pressure[70]. Sinus bradycardia with heart rate less than 50 beats per minute occurs in almost 50% of patients with PCAS during maintenance phase[71]. Nevertheless, this bradycardia should also indicate an intact physiologic response, does not require any treatment due to no hemodynamic effect and may predict good prognosis[72]. Platelets dysfunction and coagulation defect are hematologic abnormalities associated with hypothermia found in non-human experimental models[4,66]. However, abnormal bleeding associated with TTM is infrequently found in real world clinical practice[3,73]. Hypothermia also obliges kidneys to excrete water leading to volume reduction[74]. Serum potassium becomes lower during maintenance phase due to intracellular shift and renal loss however it is expected to be elevated once temperature goes up in rewarming period[4]. Serum amylase becomes elevated when temperature declines, nonetheless, this high serum amylase does not cause pathologic pancreatitis at all[75]. Although elevated blood sugar due to lower insulin level usually occurs during maintenance phase, supplementary insulin may worsen the pre-existing hypokalemia[76]. Infection, particularly pneumonia and sepsis, is a well-known adverse event in patients treated with TTM, however it is usually not associated with unfavorable outcomes[47,77].

APPLICATION OF TTM IN VARIOUS CLINICAL ENTITIES

TTM in PCAS

Combination of complex pathophysiologic process after resuscitated from cardiac arrest, known as PCAS, attribute to multiple organs damage[78]. Global ischemic cascade occurs in the brain due to generalized and severe ischemia during cardiac arrest along with reperfusion process after return of spontaneous circulation (ROSC) leading to hypoxic/ischemic brain injury[79-81]. This global brain damage is responsible for a major cause of mortality in patients with PCAS pertaining to 68% of out-of hospital cardiac arrest (OHCA) and 23% of in-hospital cardiac arrest (IHCA)[82]. TTM is a well-known neuroprotective therapy for ischemic/hypoxic brain injury[83-85].

Two landmark (RCT show that induced mild hypothermia can reduce mortality rate and improve neurologic outcome in adult patients who remained comatose after resuscitated from out-of hospital cardiac arrest and had ventricular fibrillation (VF) or ventricular tachycardia (VT) as initial cardiac rhythm[1,2]. The benefit from these two RCTs is excellent with number-needed-to-treat (NNT) 7 for avoidance of mortality and NNT 6 for favorable neurological/clinical outcomes[86]. The summary of the two landmark RCTs is revealed in Table 2. Base on the results from these two RCTs, International Liaison Committee on Resuscitation and American Heart Association declared, in 2003 and 2010 respectively, that unconscious adults who become ROSC following OHCA with VT/VF or shockable rhythm should be treated with TTM under target temperature between 32 ℃ and 34 ℃ for 12 to 24 h[6,7].

The appropriate target temperature for TTM in

Table 1 Bedside Shivering Assessment Score[69]

0	No shivering
1	Mild: Shivering confines to cervical and/or thorax only
2	Moderate: Shivering extends to whole movement of upper limbs
3	Severe: Shivering spreads to overall movement of trunk, upper limbs and lower limbs

adult patients with PCAS then becomes an important dilemma. TTM Trial is a landmark RCT for comparing benefit of TTM in adult patients after OHCA with any initial rhythm at 33 ℃ *vs* 36 ℃[87]. In November 2013, TTM Trial concludes the same benefit of neurologic outcomes and survival at six months in adult patients with OHCA treated with TTM at 33 ℃ *vs* which of 36 ℃[88]. Furthermore, at six months after discharge from the hospital, survivals in 33 ℃ and 36 ℃ group have similarly good quality of life and same level of cognitive function[89].

Clinical profit of TTM in patients with PCAS from other etiologies except OHCA with shockable rhythm remains not well-established[90]. Some small clinical trials report evidence of marginal outcomes benefit in OHCA subgroup with asystole/pulseless electrical activity, the so-called non-shockable rhythm, and also in IHCA subgroup[6,7,90]. For patients after OHCA with non-shockable rhythm, few observational studies show no difference in neurologic outcomes with TTM but possible reduction of mortality at six months[2,91,92]. A recent observational study included more than 90% of adult patients with non-shockable rhythm show improvement of neurologic outcomes and better survival to hospital discharge with TTM[73]. For patients with IHCA, few observational studies show marginal benefit of TTM in both neurologic outcomes and survival[73,93]. The most update recommendation declared by International Liaison Committee on Resuscitation, American Heart Association and European Resuscitation Council similarly state in 2015 that unconscious adult patients with ROSC after either OHCA or IHCA with either shockable or non-shockable rhythm should be treated with TTM at 32 ℃ to 36 ℃ for at least 24 h[8-10]. From the recent meta-analysis, TTM confers to better neurological outcomes than no temperature management in adult patients with PCAS, however, TTM in specific subgroup including initial non-shockable rhythm, IHCA and non-cardiac causes of arrest does not have sufficient data to make any conclusion[94]. The inclusion and exclusion criteria for TTM in adult patients with PCAS at Thammasat University Hospital are showed in Table 3.

Therapeutic Hypothermia after Paediatric Cardiac Arrest (THAPCA) Trial is a landmark study for TTM in all aspects of pediatric patients with PCAS[95]. The results from THAPCA trial demonstrated that TTM with target temperature of 33 ℃ in pediatric patients with PCAS due to either OHCA or IHCA did not show any outcomes benefit as compared with which of target temperature of 36.8 ℃[96,97].

Table 2 Summary of the landmark randomized control trials for targeted temperature management in post-cardiac arrest syndrome

	Australian trial	European trial
Sample size	*n* = 77	*n* = 275
TTM *vs* untreated	43 TTM *vs* 34 untreated	137 TTM *vs* 138 untreated
Initial rhythm	VT/VF	VT/VF
Method of TTM	Surface with ice packs	Surface with cooling blankets/pads and ice packs
Place of initiation	Emergency department	Prehospital setting
Target temperature	33 ℃	32 ℃-34 ℃
Duration of TTM	12 h	24 h
Time of Follow up	30 d	6 mo
Outcomes	NNT of 7 to avoid death	NNT of 6 to improve neurological outcomes

TTM: Targeted temperature management; VF: Ventricular fibrillation; VT: Ventricular tachycardia; NNT: Number-needed-to-treat.

TTM in ischemic stroke

In non-human experimental models with on focal brain ischemia, TTM demonstrates a very capable neuroprotective outcomes[98]. However, application of TTM in patients with ischemic stroke still has a lot of limitations[99]. Invasive endovascular method is preferred to apply in patients with acute ischemic stroke due to its feasibility and safety as reported by most clinical studies[56,100]. Under endovascular method, shivering control is convenient with non-pharmacologic skin counter-warming technique[55]. For this reason, pharmacologic anti-shivering technique which usually associated with sedative effect can be avoided[54,100]. Endovascular method is apparently not associated with bleeding complications even in post-thrombolytic condition[100]. Unfortunately, the RCT of TTM with endovascular method at 33 ℃ following intravenous recombinant plasminogen activator (rtPA) in patients with ischemic stroke (ICTuS 2 Trial) is early stopped due to the approval of interventional thrombectomy and lack of funding[101]. The sample size of ICTus 2 Trial is too small to make any conclusion on efficacy or clinical outcomes of the treatment[101].

With its reperfusion protective action, TTM should be useful to decrease symptomatic intracerebral hemorrhage (sICH) after intravenous rtPA as well as after endovascular treatment[102,103]. The landmark RCT of TTM as neuroprotective treatment with target temperature at 34 ℃ to 35 ℃ in patients with acute ischemic stroke (EuroHYP-1) is still ongoing[104]. At this moment, routine application of TTM in patients with acute ischemic stroke is not recommended[105].

Fever control with TTM technique, to keep target temperature less than 37.5 ℃, is helpful for patients with acute ischemic stroke[106]. Reduction of ICP with TTM in malignant brain infarct is demonstrated in both experimental and clinical studies[40,42,107]. TTM is helpful

Table 3 Inclusion and exclusion criteria for targeted temperature management after cardiac arrest at Thammasat University Hospital

Inclusion criteria
Witnessed arrest
Any initial rhythm, However initial rhythm VF or pulseless VT is the first priority
Time to ACLS was less than 15 min and total of ACLS time less than 60 min
GCS of 8 or below
SBP of > 90 with or without vasopressors
Less than 8 h have elapsed since ROSC
Exclusion criteria
Pregnancy
Known functional dependence
Down time of > 30 min
ACLS preformed for > 60 min
Known terminal illness
Comatose state prior to cardiac arrest
Prolonged hypotension (*i.e.*, MAP < 60 for > 30 min)
Evidence of hypoxemia for > 15 min following ROSC
Known coagulopathy that cannot be reversed

VF: Ventricular fibrillation; VT: Ventricular tachycardia; ROSC: Restored of systemic circulation.

for ICP reduction in patients with large middle cerebral artery (MCA) infarct[40]. However, routine application of TTM as ICP reduction in any type of malignant brain infarct is controversial due to insufficient support clinical data of its benefit[3,106].

TTM in TBI

Pertaining to experimental animal models for TBI, TTM provides excellent mechanism of action in both Neuroprotection and ICP reduction[108-110]. Two clinical trials in patients with severe TBI from China demonstrated good effect of TTM on ICP control with favorable outcomes after six months to one year[111,112]. Unfortunately, the following meta-analysis, which includes small to medium scale RCTs before 2003, did not demonstrate any benefit to apply TTM as neuroprotective therapy in patients with TBI[113-115]. Finally, two landmark RCTs of TTM as neuroprotective therapy in either adults or children with TBI fail to demonstrate any beneficial outcomes[70,116,117]. Elevated ICP in patients with TBI is common and associated with poor outcomes[118,119]. The previous TTM trials begin rewarming when the peak of elevated ICP occurs at around 48 h after onset of TBI leading to clinical deterioration[120]. This rebound elevated ICP found during rewarming phase is assumed to be one of the key reasons of failure in previous landmark RCT[121]. Specific group of elevated ICP in patients with TBI may get clinical profit from ICP reduction with TTM[12]. Clinical trial of TTM according to high ICP in patients with TBI was proposed[122]. Unfortunately, large scale RCT of TTM in specific TBI patients with high ICP more than 20 mmHg (Eurotherm3235 Trial) does not demonstrate any clinical benefit[123]. Recent meta-analysis of TTM *vs* normothermia in adult patients with TBI does not demonstrate any clinical benefit of TTM but reveal risk of developing pneumonia and cardiovascular complications associated with TTM[124]. Large scale RCT of TTM in particular aspects of patients with TBI is still ongoing[125]. At this moment, ordinary application of TTM in patients with TBI without clinical study is not recommended[126].

Fever controls in neurological ICU with TTM machine

Fever is commonly found in patients admitted in Neurological ICU, increases risk of complications, and is usually associated with unfavorable clinical outcomes[127,128]. For example, in patients with ischemic stroke, chance to develop poor outcomes increases 2.2 times in each one degree exceeding 37 ℃ when compared with patients who have normal temperature[129]. Most common cause of fever in Neurological ICU is infection[130]. Similar method of TTM can be applied for fever control in Neurological ICU[131,132]. The commonly use techniques such as surface and endovascular are convenient and save to employ for fever control[131,132]. Fever control in patients with septic shock with external TTM machine reduces early mortality[133]. However, overall benefit of antipyretic therapy with external TTM in patients with sepsis is still not approved[134,135]. Fever control in patients with acute ischemic stroke is recommended per standard guidelines[105].

TTM in other clinical entities

TTM can apply as organ protective therapy from ischemic effect during cardiovascular surgery with circulatory arrest[136,137]. The landmark RCT of TTM for the period of operation in patients with benign grade SAH from ruptured intracranial aneurysm (World Federation of Neurological Surgeons scale between one and three) did not show any clinical benefit with more frequent associated infection[138]. TTM can reduce perilesional edema with favorable outcomes in animal models with intracerebral hemorrhage (ICH)[139]. The TTM after intracerebral hemorrhage (TTM-ICH) trial is ongoing[140]. At this moment, routine use of TTM in patients with ICH is not recommended[141]. The prospective protocol-selected trial demonstrated potential clinical benefit of local TTM in patients with neurologically complete spinal cord injury[142]. Experts recommend that TTM can be the option for ICP control in patients with fulminant hepatic encephalopathy particularly while waiting for liver transplantation[143].

Application of TTM in donors demonstrates organ protective effect on kidney in recipients[144]. This RCT is the first ever for clinical trial which demonstrates organ defensive action of TTM from hypoxic/ischemic cascade outside the brain. The process of TTM at 34 ℃-35 ℃ in kidney donors in this study is convenient and the cost of treatment is economic[145]. TTM in kidney donors can be its second class Ⅰ recommendation per standard guidelines following post-cardiac arrest in the near future.

CONCLUSION

Two main purposes of TTM in patients admitted in Neurological ICU are neuroprotective therapy and ICP control. TTM is the most potent neuroprotective treatment due to its numerous effects against ischemic/hypoxic injury. TTM provides reliable ICP reductive action. Two most popular methods of TTM using in clinical practice and clinical trials are invasive endovascular technique and non-invasive surface cooling. Fast induction, smooth maintenance and slow rewarming are the important steps to achieve ideal TTM. The strongest clinical benefit of TTM is the excellent outcomes with neuroprotective effect in patients with PCAS. TTM has been recommended as the essential treatment for OHCA with shockable rhythm for more than 10 years. Even with marginal benefit, TTM is still recommended for non-shockable rhythm and IHCA subgroup. TTM may give benefit in patients with acute ischemic stroke however its role needs to be proved with large scale RCT. TTM should be clinically useful for ICP reduction in patients with malignant MCA infarct. Routine use of TTM in patients with TBI as neuroprotective therapy or ICP control is still not recommended due to lacking of any benefit from many RCTs. TTM machine can be applied as fever control in patients with various conditions in Neurological ICU. Fever control should help to improve clinical outcomes in patients admitted in Neurological ICU.

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