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Artigo Original

Protocol to the induction of loco-regional mild hypothermia for temporay clipping in the surgery of the middle cerebral artery aneurysm

Protocolo para a indução de hipotermia moderada loco-regional para a clipagem temporária dos aneurismas da artréria cerebral media

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ABSTRACT

Introduction: *Less than 30% of Middle Cerebral Artery (MCA) aneurysms are amenable for endovascular coiling. Microvascular surgery still carries a large number of complications, since many perforators arteries arise near to the neck of the aneurysm and, in many cases, one or more branches of bifurcation or trifurcation of the MCA originate in the aneurysm wall. Temporary clipping of the proximal MCA avoids the aneurysmal rupture, facilitates the aneurysm dissection and clip placement but long term temporary clipping carries a great risk of ischemic complications.* ***Objective:*** *We developed a protocol of brain protection based on the neuroprotective properties of mild hypothermia which would intend to permit a more extended time of temporary clipping.* ***Methods:*** *Sixty-eight cases of MCA incidental aneurysms or after the 12nd day of hemorrhage were operated on. Brain temperature was dropped at levels that varied from 29.5ºC at 15mm parenchymal depth to 32.5ºC at ventricular level. There was no change in the patient's body temperature. Temporary MCA clipping varied from 8 to 28 minutes.* ***Results:*** *There was no intraoperative aneurysm rupture. All 68 patients were alive and neurologically unchanged at the 90th and 180th follow-up days.* ***Conclusion:*** *Loco-regional mild hypothermia may be effective in protecting cerebral parenchyma in cases of temporary clipping over 8 minutes up to 28 minutes in MCA aneurysms surgery.* ***Key-words:*** *Brain protection. Brain hypothermia. Temporary clipping. Aneurysm surgery.*

SUMÁRIO

Introdução: *Menos de 30% dos aneurismas originados na artéria cerebral média são passíveis de embolização endovascular. A clipagem por microcirurgia vascular ainda apresenta um considerável número de complicações, uma vez que vários ramos perfurantes se originam nas proximidades do colo aneurismático e, em muitos casos, um ou mais ramos da bifurcação ou trifurcação da artéria cerebral média (ACM) têm origem na própria parede do aneurisma. A clipagem temporária da porção proximal da ACM evita a ruptura do aneurisma e facilita a dissecção do mesmo, assim como a colocação do clipe. Sabe-se, entretanto, que um período muito longo de clipagem temporária apresenta um grande risco de complicações isquêmicas.* ***Objetivos:*** *Nós desenvolvemos um protocolo de proteção, baseado nas propriedades neuroprotetoras da hipotermia moderada, objetivando o prolongamento, sem complicações, do período de clipagem temporária.* ***Métodos:*** *Sessenta e oito casos de aneurismas incidentais da ACM ou após o 12º dia pós-sangramento foram operados. A temperatura cerebral foi reduzida a níveis que variaram de 29.5ºC a 15mm de profundidade do parênquima, atingindo 32.5ºC a nível ventricular. A temperatura corporal dos pacientes manteve-se inalterada. A clipagem temporária da ACM variou de 8 a 28 minutos.* ***Resultados:*** *Não tivemos ruptura aneurismática intraoperatória. Todos os 68 pacientes encontravam-se vivos e sem piora do quadro neurológico decorridos 90 e 180 dias após a cirurgia.* ***Conclusões:*** *A hipotermia loco-regional moderada pode ser útil na proteção do parênquima cerebral em casos de clipagem temporária de 8 minutos a 28 minutos em cirurgias de aneurismas da ACM.* ***Palavras chave:*** *Proteção cerebral. Hipotermia cerebral. Clipagem temporária Cirurgia de aneurismas.*

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Introduction

Aneurysm surgery is still a great challenge for neurosurgeons and neuro-interventionists. Middle Cerebral Artery (MCA) aneurysms are the ones that mostly require the ideal conditions for surgical treatment, since less than 30% are amenable for endovascular coiling.

Large number of publications demonstrated that MCA surgery has a great risk of complications, since important perforators vessels have their origin near the aneurysm neck or in the aneurysm wall. Even more, in many cases, one of the branches of the MCA bifurcation originates in the aneurysm wall itself, what makes endovascular coiling very risky. In several publications an unfavorable impact on outcome from intraoperative aneurysmal rupture has been reported[2,9,21].

The use of temporary clipping has been widely advocated by several neurovascular centers[2,9,21,28]. Temporary clipping of the proximal MCA facilitates the aneurysm and perforators vessels dissection as well as clip placement, avoiding the rupture of the aneurysm, a disastrous intercurrence which may cause, very often, a narrowing of MCA lumen after permanent clipping as well as increasing the risk of cerebral vasospasm, with permanent deficits[2,9,21,28].

Corporal mild hypothermia has demonstrated to have neuroprotective effects in cases of arterial circulatory arrest[25]. However when the body temperature is lowered below 35ºC, some deleterious effects may occur[12,11,27,8,24].

Based on hundreds of publications referring the neuroprotective properties of mild hypothermia, we undertake its use in many surgical procedures, including brain tumor removal, brain edema reduction and in every aneurysm surgery. We present our protocol of loco-regional mild hypothermia for MCA surgery. The method intends to promote neuroprotection, allowing a more extended period of safe temporary clipping. The aneurysm and perforators can be better dissected as well as clip placement may be facilitated, since the pressure inside the aneurysm may be considerably reduced. The patient's body temperature is maintained at normal levels.

Methods

This was a multicentric prospective study. The doctors involved are neurosurgeons working in many neurosurgical centers in Brazil*. The senior author (MNP) has participated in every surgery. Dates were centralized at the Federal University of São Paulo. Although surgeries concerning to all types of aneurysm have received neuroprotection with hypothermia, the present protocol was restricted to MCA aneurysms. A total of 68 MCA aneurysms were operated on in a ten-years spam. Fifty seven patients were in Hunt&Hess grade I or II. Eight patients were in Hunt&Hess III due to severe hemiparesis or hemiplegia. Eight patients had intraparenchymal hematoma at surgery. Temporary clipping of the proximal MCA varied from 8 to 28 minutes. The number expresses the total spam of time of temporary clipping. One single temporary clipping varied from 4 to 22 minutes. There was a female predominance in a proportion of 63% to 27% and the age varied from 23 to 72 years-old. All aneurysms were operated on after the 12nd day of hemorrhage or were incidental. Three patients harboring MCA aneurysm that demonstrated signals of severe arterial disease were not included into the protocol. We decided that no more than 3 minutes of temporary clipping should be performed in such cases.

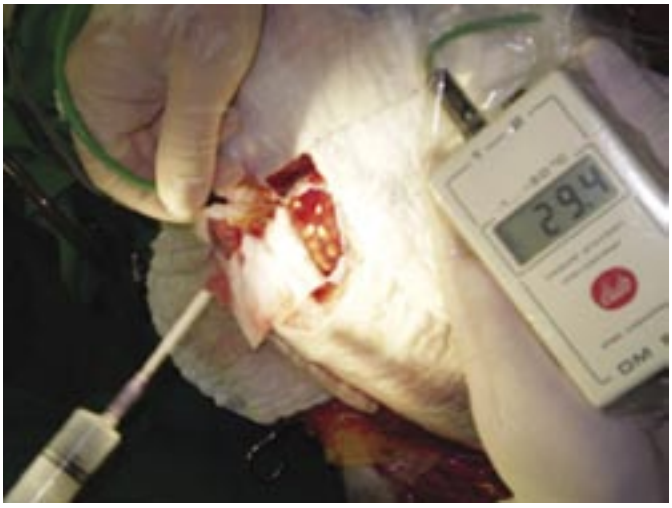

Fig. 1: Thermometer probe inserted 15mm deep in brain parenchyma. The temperature is 29.4ºC.

To reduce the temperature of the cerebral parenchyma a large craniotomy is performed. As soon as the bone is removed, a solution of 500ml of saline at 11ºC and 2ml of 5% chloride of papaverin is continuously dropped in order to wash the surface of the dura. After dural opening, a large piece of cotton is placed covering the entire exposed brain cortex and the solution is washed until the temperature of the parenchyma at 15mm depth is reduced to 29.5ºC - 30,5ºC (Fig.1). The solution is continuously dropped until the aneurysm is localized. At this point the temperature is again checked and the aneurysm dissection is performed after the temporary clip is placed in the proximal MCA as close as possible to the aneurysm neck. The temporary clip is removed after the permanent clip is adjusted. In case of need of permanent clip replacement, another temporary clipping could be done if necessary.

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Jornal Brasileiro de Neurocirurgia

Washing is discontinued when the dura is totally closed.

Results

A series of 68 MCA aneurysms were operated on. There was no aneurysmal rupture at surgery. No one patient presented neurological worsening after operation. Four patients were hemiplegic at six months follow up but hemiplegia was present prior to the operation. Other 64 cases presented only mild or did not have any neurological symptoms at all at three and six months follow up.

Discussion

In 1956 Rosomoff reported that deep hypothermia (23ºC) reduced ischemic damage after experimental occlusion of the middle cerebral artery in dogs[25]. Deep hypothermia became an adjuvant method for neuroprotection in cases where circulatory arrest in complex aneurysm surgery was necessary. However the detrimental effects of prolonged deep hypothermia including delayed recovery from anesthesia, acidosis, hemodynamic compromise, blood hypercoagulability, hypotension and myocardial arrhythmia have limited the use the technique[8,11,12,27].

Over the last 20 years a large number of studies have demonstrated that mild hypothermia (31-33ºC) can have the same neuroprotective effect provided by deep hypothermia in ischemic brain[1,2,3,5,6,9,14,16,19,20,22,21,28].

The mechanisms underlying this neuroprotection have been attributed to several mechanisms like a decrease in cerebral metabolic oxygen demand and reduction of glycine and excitatory aminoacid (EAA) release. Glutamate release occurs 1-5 h after ischemic onset and mild hypothermia can be protective even if delayed by 2 hours[14]. Corbett et al.[6] demonstrated that delayed hypothermia reduces focal ischemic injury. Therefore, although reducing EAA release[3] and glycine and glutamate release[14], mild hypothermia can have other neuroprotective effects other than EEA, glutamate and glycine release. Even more, while neuroprotection by deep hypothermia can be explained by a decrease in cerebral blood flow and metabolic demand for oxygen, this by itself cannot fully explain the equal protection that has been shown when the temperature is lowered by only a few degrees,[17]. A high degree of neuroprotection was conferred by postischemic cooling (2h) to 32ºC which is virtually equivalent to that observed with intraischemic cooling at the same level in focal cerebral ischemia4 Nakano et al. have demonstrated the neuroprotective effect of mild hypothermia in the temporary brain ischemia in cats[20]. Hypothermia was induced with an ice bag over the chest/abdomen. Brains were stained with triphenyltetrazolium (TTC) and ischemic volume was determined according to the lack of stained area. Avoiding the detrimental effects of corporal cooling, the method of loco-regional brain hypothermia has demonstrated to be very useful in reducing brain insults of most variable origins. In 2002, Prandini et al.[22] have already demonstrated that loco-regional mild hypothermia (30ºC) can be produced by covering the scalp of rabbits with ice bags, after removal of some portion of the skull bone. The neuroprotective effects in ischemic lesions induced by the coagulation of the middle cerebral artery could be demonstrated on the bases of the method of TTC staining (fig 2 a, b).

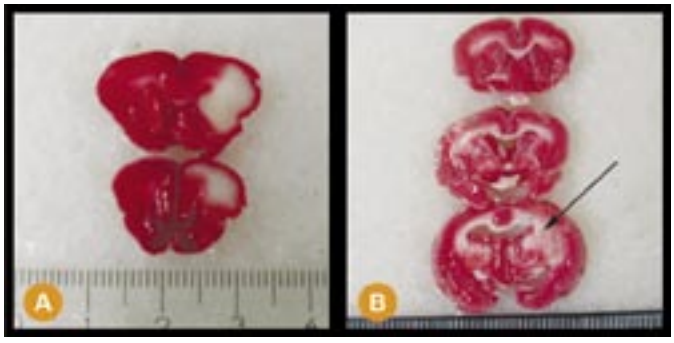

Fig. 2: Brain rabbit section stained with TTC. (A) No hypothermia protection. Infarcted area can be seen (white arrows) (B) Hypothermia protection. Only small infarcted area can be seen (black arrow).

It has been documented that inflammation contributes significantly to cerebral injury following ischemia[7]. Inflammatory cells presumably promote ischemic cell damage by microvascular occlusion. This may prolong and intensify the ischemic event[10] Cytotoxic inflammatory reactions caused by microglial activation and blood-borne neutrophil have been implicated in the pathogenesis of ischemia/reperfusion brain injury[4,7,13,18]; neutrophil began to infiltrate into an infarcted area soon after ischemia. Cytokine expression may be the earliest sign of the inflammatory response: cytokines activate microglia and stimulate expression of endothelial adhesion leading to leukocyte infiltration. PMNL accumulation is maximal at 48-72h. Attenuation of the inflammatory response may be one of the mechanisms by which hypothermia reduces ischemic neuronal injury[17,18,30,31].

Sprumont et al[26] have demonstrated the effects of neurotropin on cerebral edema, calcium and other elements in mice subaracnoidally injected with carrageenan. Prandini et al[23] have demonstrated that induced inflammation with topical carrageenan in brains of mice could be reduced by hypothermia, after hemi-craniectomy and placement of ice bags covering the enti-

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Jornal Brasileiro de Neurocirurgia

re skull. (fig. 3 a, b). Dvilevitius and Prandini have demonstrated that mild hypothermia had protective effects in brain trauma in mice, provoked by controlled impact. The hypothermia was induced with ice bags covering the entire skull, soon after the impact, produced by a device specially designed**. Forte and Prandini*** have studied 23 cases of malignant intracranial hypertension resistant to all traditional therapeutic measures in a neurologic intensive care unit. After decompressive craniectomy, loco-regional hypothermia was induced with the placement of ice bags covering the scalp. An important reduction of the intracranial pressure levels could be statistically demonstrated.

In aneurysm surgery, the temperature of the brain parenchyma can be reduced to 29,5ºC - 30ºC at 15mm depth and to 31ºC - 32ºC at 25mm depth if the saline solution at 11ºC is continuously washed on the operating field after the dural opening. The ventricular temperature can be maintained at 32,5ºC but in some particularly more difficult cases, after the lamina terminalis opening, the intraventricular injection of the same solution at 20ºC - 22ºC or even lower, promotes the reduction of intraventricular temperature so that the whole brain temperature can be more intensively reduced. The body temperature is always maintained at normal temperature, without the deleterious effects resulting of the corporal temperature reduction [11,12,25,27].

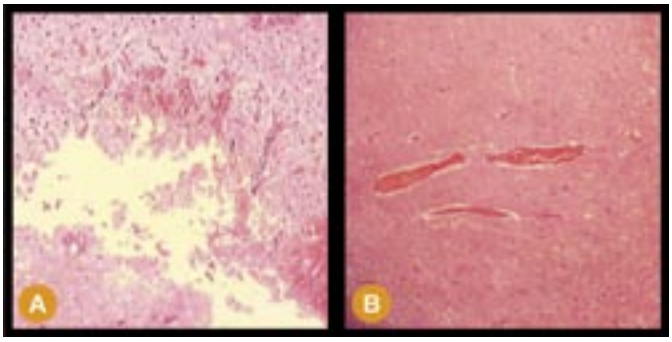

Fig. 3: (A) Rat brain. Haematoxylin-eosin 200X. Slices obtained three days after Carrageenan was dropped. No neuroprotection was performed. Small necrotic area and marked inflammatory infiltration can be seen. (B) Rat brain. Haematoxylin-eosin 100X. Neuroprotection with mild hypothermia (30ºC) for 120 minutes. There is moderate vascular congestion.

Intraoperative rupture of aneurysms accounts for most of all technical problems encountered in large studied series and permanent injury resulted from more than 1/5 of ruptures[2]. Temporary clipping can help greatly in handing a fragile dome and eases clip placement,[2,9,21,28]. We had no aneurysm rupture. Our cases were not operated on soon after hemorrhage and this may have favorably influenced our results: it was a multicentric study, carried out in many cities with many technical difficulties so we decided to include only incidental aneurysms or ruptured aneurysm cases after the 14th day of bleeding.

Stroke is an expected complication in aneurysm surgery since intraoperative stroke in the range of 5 to 10% is reported[2,29] One of the two cases of MCA that were not included into the protocol where temporary clipping lasted for less than three minutes developed a brain infarct, resulting in a permanent hemiplegia. We had one case of mortality regarding the total series of anterior territory aneurysms. It was a unique case. She was a 42-year-old patient that one year before was admitted in another institution presenting an ischemic stroke. After having partially recovered, she was referred to us. At first we were reluctant in deciding for surgical clipping but coiling was not possible due to the aneurysm characteristics. The aneurysm was situated in the proximal MCA and many perforators originated from the aneurysm wall. At surgery many ateromatous plaques were identified in the carotid and MCA territories. It was the only case where a trapping was necessary in order to better dissect the several perforators that originated from the aneurysm wall. We suppose that brain infarct was caused by the ischemia resultant from the temporary circulatory arrest.

Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST)[29] has studied a total of 1001 patients that were randomly assigned to intraoperative hypothermia (target temperature, 33ºC, with the use of surface cooling techniques) or normothermia (target temperature, 36.5ºC). There were no significant differences between the group assigned to intraoperative hypothermia and the group assigned to normothermia. Our protocol differs substantially from this trial: we were focused only in the MCA aneurysm, our patients were operated on after 14 days of hemorrhage and not before, the body temperature was maintained at normal levels and brain temperature could be maintained at least 3 degrees below the temperature reported on the IHAST. Our main purpose was to promote neuroprotection, keeping the corporal temperature at normal levels, since the main complications of hypothermia are related to the drop in the body temperature.

Conclusion

Our protocol only intends to offer a possibility of promoting some sort of neuroprotection, in a very simple way, in cases of aneurysms surgery, permitting a more extended spam of temporary clipping. MCA aneurysms have special characteristics that either treated by microsurgery or endovascular embolization always carry some sort of risk. In this way, temporary clipping may be of value in reducing intraoperative aneurysm rupture and facilitate permanent clip application. Over the last years, several neuroprotective drugs have been on trial and it is likely

soon they will be ready to be used. Induction of mild hypothermia probably will no interfere with their use and we hope will only benefit other neuroprotective supportive agents.

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