

Title: MULTIFACETED (MF) THERAPY AFTER GLOBAL BRAIN ISCHEMIA (GBI) IN MONKEYS

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**Introduction.** Resuscitation (i.e. post-insult therapy) of the brain after GBI has great socio-economic importance. Hypothermia can ameliorate focal ischemia (1). Hypertension plus hemodilution appears promising after GBI (2). Steroid after GBI has not been studied. Thiopental loading ameliorated brain damage after GBI in rhesus monkeys (3), but not in pigtail monkeys (4). Barbiturates reduce metabolism and ICP (5). They can increase survival by suppressing seizures without improving quality of survival (6). The pathophysiology of postischemic (PI) encephalopathy is multifactorial. Identified changes PI include: tissue acidosis and edema; multifocal hypoperfusion (sludging, clotting, vasospasm); hypermetabolism; membrane damage, and failure of energy production. Thus, this study was designed to test the hypothesis that PI therapy is more likely to be effective if it is multifaceted. Each of the treatments tested in combination here, might ameliorate one or more of the above changes.

**Methods.** We used the high pressure neck tourniquet model of GBI (18 min) (3,4,7) in pigtail monkeys, with concurrent controls. Completeness of ischemia had been verified by radio tracers and angiography, and was ascertained from EEG silence, facial pallor and retinoscopy. Upon cuff release, normotension was restored within 2 min. MAP control was by titration of norepinephrine or trimethaphan IV. Control treatment included PI paralysis, 50% N<sub>2</sub>O at 2-24h PI, IPPV 24h (PaCO<sub>2</sub> 25 torr), PaO<sub>2</sub>>100 torr, normothermia, fluid balance, seizure prophylaxis with phenytoin starting at 20h PI, and continuous intensive care for 96h. The multifaceted treatment tested consisted of the control treatment (above) plus a combination of: (1) hemodilution (HD) with 5% albumin to hct 25% through an aortic arch catheter (for carotid perfusion) at 1-4 min PI; (2) hypertension with MAP 130 torr for 5 min after HD, normotension thereafter; (3) hypothermia by surface cooling of 30°C for 2h starting at 10 min PI; (4) pentobarbital 30 mg/kg IV at 20-150 min PI; and (5) dexamethasone 2 mg/kg IV at 3-10 min PI and at 90-100 min PI. Outcome was evaluated by 3 methods: (1) Final neurologic deficit (ND) scoring (ND 100%=brain death, 0%-normal) (4,7) at 96h PI. (2) Overall performance categories (OPC) at 96h determined from ND scores plus prolonged observation of the animal's performance and behavior (OPC 1=normal; 2=slight disability; 3=conscious with severe disability; 4=unresponsive, vegetative state; 5=brain death,

death). (3) Perfusion fixation sacrifice and brain removal followed by neurohistologic examination of 20 brain regions, and scoring of microinfarcts, ischemic neuronal changes, and edema (3,4,7).

**Results.** 9 monkeys with standard therapy and 10 with multifaceted therapy followed protocol (no errors). ND scores at 96h PI were 36±27% after control therapy, and 23±15% after multifaceted therapy (NS). OPC 1-2 (awake) at 96h PI was reached by 2/9 monkeys in the control group, and by 7/10 monkeys in the multifaceted therapy group (p<0.05). 1/9 controls vs 0/10 of MF group reached OPC 5; and 6/9 controls vs 3/10 of MF group OPC 4 (vegetative state) at 96h. The incidence of mild seizures late PI was the same in both groups. Histologic data are under analysis and will be reported.

**Conclusions.** This combination treatment was chosen to improve reperfusion, reduce metabolism, stabilize membranes and improve energy production. Outcome data with this multifaceted therapy vs standard therapy alone seem promising for brain resuscitation after GBI and support the above hypothesis. This should be restudied in a total circulatory arrest model, and if effective, without hypothermia, which is clinically more complex and hazardous than the other treatments of this combination.

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