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EFFECT OF LOCAL COOLING (15° C FOR 24 HOURS) WITH THE CHILLERPAD™ AFTER TRAUMATIC BRAIN INJURY IN THE NONHUMAN PRIMATE

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1. INTRODUCTION

The efficacy of hypothermia is proven in rats [1] but unproven clinically in traumatic brain injury (TBI)[2] . Despite the failure of the NIH supported multicenter clinical trial to show improved outcome with hypothermia [3], optimism about the potential efficacy of hypothermia persists because of the delay of eight to twelve hours before the induction of hypothermia in the clinical trial. Furthermore, a subgroup analysis from that study showed that younger patients with TBI who received hypothermia and who were not rewarmed, had better outcome [2].

Our aim in this study was to evaluate the efficacy of hypothermia induced directly on the cerebral cortex using the ChillerPad™ to 15° C for 24 h beginning three hours after TBI in the Rhesus monkey (M. mulatta) with recovery for ten days after TBI.

2. METHODS

2.1 Surgical Procedures

Following a protocol approved by the Institutional Animal Care and Use Committee, six male monkeys (M. mulatta) weighing from 5.0 to 9.3 kg, (7.3 ± 5.1, mean ± SD) were intubated and mechanically ventilated on isoflurane/70% nitrous oxide/30% oxygen for anesthesia. A femoral artery catheter was inserted and the monkeys turned prone for head fixation in a stereotactic device. The dorsal calvarium was scrubbed with betadine for aseptic surgery. A circular craniotomy 22 mm in diameter was centered 3.5 cm from the orbital ridge. An intracranial pressure transducer (Camino 110-4G, Integra) was

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inserted subdurally adjacent to the craniotomy through a 3-mm burr hole and secured in place with a cyanoacrylate glue-soaked sponge.

2.2 Controlled Cortical Impact (CCI)

A controlled cortical impact (CCI) was produced at a velocity of 3.5 m/sec and a depth of penetration of 7 mm from the cortical surface at the peak of inspiration as judged by the end-tidal CO_2 pressure wave. Immediately after the CCI, which generally caused a tear in the dura, the dura was sutured with 6-0 prolene, the bone flap replaced and secured in place by suturing the galeoperiosteal flap over the bone flap for the three hour delay before the placement of the ChillerPad™ and the start of cooling the brain to 15° C.

2.3 Cooling and Rewarming

Beginning at 2.5 h after the CCI, the craniotomy was exposed and the ChillerPad™ was placed onto the dura with thermocouples in the center beneath the ChillerPad™. The ChillerPad™ was secured in place by suturing the galeoperiosteal flap over it and over that, the skin. Throughout the 24 h cooling period and 10 h of rewarming at 2.5° C/h, physiological variables were continuously monitored with intermittent monitoring of arterial blood gases and electrolytes. Electrolytes were maintained within normal limits by switching to plasmalyte with the addition of potassium if necessary. Fluid intake and urine output were monitored with adjustments in the fluid infusion rate to balance to a net positive uptake of about 300 ml over the 24 h of cooling and 10 h of rewarming.

After complete rewarming, the ChillerPad was removed and thecraniotomy was sealed with the bone flap which was cemented in place with methylmethacrylate cement. The skin was sutured subcutaneously and the monkey treated prophylactically with 250 mg Cefazolin, i.v. Anesthesia was switched from isoflurane/nitrous oxide/oxygen to ketamine and fentanyl, the latter by continuous infusion with continuous monitoring of noninvasive arterial blood pressure.

2.4 Magnetic Resonance Imaging

The monkey was transported to the MRI scanner for a 40 hr post TBI MRI scan with SPGR, proton and T2 weighted scanning and diffusion tensor scanning. The MRI scan was done using a 3.0T GE scanner.

2.5 Recovery

After completion of the MRI scan, the monkey was returned to the OR where it recovered from fentanyl anesthesia by washout rather than reversal with Narcan and placed into the recovery room. The monkey was observed continuously for the next 24 h of recovery before being placed in the normal holding facility. Analgesia was provided with Buprenorphine after the first 24 h of recovery to avoid depressing the monkey with sedation in the early postrecovery period.

Neurologic examinations were done daily over the 10 days of recovery. Repeat MRI scans were performed at 4, 7 and 10 days. In some cases, the day 4 MRI was not done because it was felt that because the monkeys had gone 3 days without food and after recovering for 24 hr again placed on NPO, would be too much of a stress. Therefore, two monkeys did not have an MRI on day four post TBI.