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TITLE: PROTECTIVE EFFECT OF KETAMINE FOLLOWING CLOSED CRANIAL IMPACT IN RATS

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Introduction: We previously reported that the NMDA receptor antagonist MK-801 improved brain tissue specific gravity (SG) and neurological severity score (NSS) after head trauma in rats.[1] While our results suggest that MK-801 may be beneficial for patients with head trauma, MK-801 is not approved for clinical use. Ketamine (K) also is an NMDA receptor antagonist, is approved for clinical use and previously was reported to improve neurological outcome after ischemia. The present study was designed to determine whether K, like MK-801, improves neurological outcome following head trauma in rats.

Material and Methods: This project was approved by the institutional Animal Care Committee. Twenty-three male Sprague-Dawley rats (235-250 g) were randomly divided into 4 groups (Gr). Gr 1 and 2 underwent sham operation and Gr 3 and 4 underwent operation and head trauma. Gr 1 and 2 received no treatment. Gr 2 and 4 were treated with K, 180 mg/kg ip, 1 h after head trauma. NSS was estimated 1, 2, 4, 10, 24 and 48 h following head trauma using a scale where 0 = intact neurologic status and 23 = maximum functional impairment. After sacrifice at 48 h, cortical slices were taken adjacent to the lesion on the traumatized hemisphere and from comparable sites on the nontraumatized hemisphere to measure tissue specific gravity (SG) and H_2O% as estimates of edema formation. Brains were then placed in formaldehyde and infarct volume measured 6 days later.

Results: Head trauma decreased NSS and, on the traumatized hemisphere, decreased SG, increased H_2O% and caused cerebral infarction. With K, NSS at 24 and 48 h following head trauma was 7.4 ± 2.6 and 6.7 ± 2.6 (mean ± SD), significantly improved compared to NSS in the untreated Gr, 12.6 ± 2.6 and 11.3 ± 2.6 ($p < 0.02$, Mann-Whitney U test). With K, the infarct volume was 169.33 ± 44.50 mm^3, significantly less than that in the untreated Gr, 283.38 ± 43.03 mm^3 ($p < 0.05$, unpaired T test). On the traumatized hemisphere SG and H2O% were not statistically different with K (1.0380 ± 0.0016 and 83.65 ± 1.24%) as compared to the untreated Gr (1.0381 ± 0.0034 and 84.55 ± 1.19%). Rectal temperature at 4 and 48 h after head trauma ranged from 36.4 ± 0.1 to 36.5 ± 0.1 °C and was not significantly different between Gr.

Conclusions: K, like MK-801 improves NSS without decreasing brain edema formation during the first 48 h following head trauma. Improvement of NSS and decrease of cerebral infarct volume with K suggests that trials should be undertaken to determine if K is suitable for use in patients with head trauma.

Reference:
1. J Neurotrauma 3:131-139, 1990

A204

Title: NEUROLOGICAL STATUS AND BRAIN EDEMA FOLLOWING CLOSED CRANIAL INJURY IN RATS IS UNAFFECTED BY HIGH QUANTITY GLUCOSE AND FLUID ADMINISTRATION

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Following closed cranial injury (CCI), patients traditionally are treated by restriction of fluid and glucose intake. While certain studies support this treatment approach, other clinical studies and non-impact models of cerebral injury (such as cold injury) in animals question the efficacy of fluid and glucose restriction following neurological injury. The present studies employed a blunt-impact model of CCI to examine, under controlled conditions, the effect of large volumes of iv solutions, with and without glucose, on neurological status and brain edema following CCI.

Fifty-five male sabra rats (328 ± 37 g, mean ± SD) underwent standard left hemisphere CCI (1). Animals surviving the first 5 min after CCI were randomly divided into 5 groups. Four groups underwent jugular vein cannulation for fluid infusion. Three groups were infused with 10 cc/kg/hr of either A) total parenteral nutrition (TPN), B) dextrose 5% in 0.45% NaCl or C) Haemecel. In the fourth group minimal amounts of saline were infused at the time the cannula was inserted. In the fifth group the jugular vein was not cannulated. Neurological severity score (NSS) was determined at 1 h and 18 h post injury. At 18 h all rats were decapitated, blood samples collected for analysis, and edema of both hemispheres estimated by tissue specific gravity (SG) using linear gradient columns.

There was no significant difference in NSS between the experimental groups at 1 h or 18 h post injury. The combined mean NSS (100% represents the most severe neurological damage) of all groups was 46 ± 20% at 1 h post injury. The combined mean NSS of all groups at 18 h, 30 ± 26%, was significantly decreased (less neurological damage) compared to that at 1 h. Left (traumatized) hemisphere SG ranged from 1.0384 ± 0.0016 to 1.0398 ± 0.0020 and was not significantly different between groups at 18 h post injury. In all groups left hemisphere SG was decreased compared to right hemisphere SG (1.0421 ± 0.0019 to 1.0427 ± 0.0020), indicating that CCI caused cerebral edema. Urine output was increased in the three groups receiving 10 cc/kg/hr iv fluid, and blood glucose (17.5 ± 4.2 mmol/L) was increased in the TPN group.

It is concluded that both infusion of large volumes of isotonic or hypertonic fluids or administration of glucose iv (with or without increase of blood glucose values) does not affect NSS or brain edema after CCI in rats.

Reference
1. Crit Care Med 16:258-265, 1988