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# COMPARISON OF THE EFFECTS OF MANNITOL AND DEXAMETHASONE ON THE HYPOXIC BRAIN EDEMA(*) (Part-II)

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**SUMMARY:**

In this second part of the experiment, hypoxic-hypoxia insults in the cerebellum were investigated with the effects of mannitol and dexamethasone, alone and in combination, on the secondary chemical alterations. Because of the moderate hypoxic-hypoxia, chemical alterations were not compatible with the neuronal alterations observed by electron microscopy which was parallel to the literatüre. In conclusion, mannitol was found to be the most effective on water content in moderate hypoxic-hypoxia brain insults, dexamethasone taking the second rank.

## INTRODUCTION

In the first part of the experiment, hemispheric water and electrolytes changes in the hypoxic–ischemic brain edema were studied, but in this second part of the study, the same changes in the cerebellar tissue of the same rats used in the experiment were studied and reported. As well known, cerebellar circulation is independent of the antrerior cerebral circulation, therefore cerebellar samples used here should have been affected by the only hypoxia not the ischemia which produced in the study with ligation of a common carotid artery.(9).

Types of brain ischemia were classified by BRIERLEY (5) and he showed that the pattern of brain damage secondary to the hypoxic–hypoxia was indistinguishable from that produced by oligemic–hypoxia. Therefore ADAMS suggested that hypoxic and ischemic brain damages can be taken as synonymous since the basic abnormality being the same which is the inadequate supply of oxygen to the neurones (1, 33). In this part of the study, the effect of hypoxic–hypoxia, which produced by atmospheric decompression (9), on the cerebellar tissue water and electrolytes and also upon those changes the effects of mannitol, dexamethasone alone and in combination have been the main subject.

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Key words: Mannitol, Dexamethasone, Brain edema, Rat, Hypoxia.

## MATERIALS AND METHODS

In the first part of the study, the rats in the experiment were divided into A and B experimental groups each of which was also further subdivided to CONTROL and TREATED groups. In this part of the study, therefore, cerebellar samples were taken from the rats in the CONTROL and TREATED of both A and B experimental groups. The samples taken from the control groups' rats served as CONTROL–hypoxic cerebellum– and the samples from the treated groups served as MANNITOL TREATED (M), DEXAMETHASONE TREATED (D) and MANNITOL–DEXAMETHASONE TREATED (DM) groups. The number of rats for cerebellar samples were displayed in the related tables no: 1 /2 /3.

Following all the procedures applied for the experiment, which was explained in detail in the first part of the study, cerebellar hemispheres were inspected which were both swollen as the cerebral hemispheres. Then samples were taken from the cerebellum of each rats and they were placed in the known weighed pots which were then reweighed for wet tissue weight of the cerebellar parts. All pots were placed in an oven for 48 $\mp$ 2 hours to dry cerebellar samples. The water content of each sample was calculated from the difference in the wet and dry weights.

Dried cerebellar parts were digested with 0.75M HNO3 for 24 hours. After centrifugation of the mixture, the supernatant was taken and $Na^+$ and $K^+$ ion concentrations were measured with a flame photometer. Ion concentrations were calculated in mEq /kg wet tissue.

## RESULTS

*$Na^+$ concentrations:* Mean $Na^+$ concentrations of the control and treated groups' rats and also comparison results of the combined groups are displayed in Table–1 and Figure–1. Kruskall–Wallis' variance analysis showed that values in the 3 treated groups were statistically different ($KW = 14.152$, $df = 2$, $\alpha = 0.01$, $X^2 = 9.210$, $p < 0.01$). To be different was account of that $Na^+$ values in both MANNITOL and DEXAMETHASONE TREATED groups were insignificantly increasing, while it was significantly decreasing in MANNITOL–DEXAMETHASONE TREATED group upon comparison to the CONTROL group. Accordingly with these observations, the effects of mannitol and dexamethasone were appeared to be indifferent each other; additionally, when both mannitol and dexamethasone was separately

compared with the mannitol–dexamethasone combined group, statistical difference was found to be highly significant, being $p < 0.01$ for both compared groups.

Table 1. Comparison of the mean values of $Na^+$ concentrations of cerebellar tissue in the treated and control groups (n: number of rats).

| TREATED GROUPS (with mean values) | COMPARED GROUPS | |
|---|---|---|
| | Control / Mannitol | Control / Dexamethasone |
| Mannitol (n:18) 49.02 ∓ 4.10 | t=0.852 p>0.05 | t=0.376 p>0.05 |
| | Control / Mannitol-Dexamethasone | Mannitol / Dexamethasone |
| Dexamethasone (n:18) 48.05∓5.78 | t=2.093 p<0.05 | t=0.581 p>0.05 |
| | Dexamethasone / Mannitol-Dexamethasone | Mannitol / Mannitol-Dexamethasone |
| Mannitol-Dexamethasone (n:18) 42.35∓4.97 | t=3.172 p<0.01 | t=4.392 p<0.01 |
| Control Group (n:18) 47.15∓10.05 | | |

*$K^+$ concentrations:* When 3 treated groups were analysed in the similar way of Na evaluation, a significant KW value was calculated (KW = 20.186, df = 2, $\alpha = 0.01$, $X^2 = 9.210$, $p < 0.01$). As seen in Table–2, the effects of mannitol and dexamethasone were similar to each other, both decreas

Table 2. Comparison of the mean values of $K^+$ concentrations of cerebellar tissue in the treated and control groups (n: number of rats).

| TREATED GROUPS (with mean values) | COMPARED GROUPS | |
|---|---|---|
| | Control / Mannitol | Control / Dexamethasone |
| Mannitol (n:18) 87.05∓7.87 | t=3.281 p<0.01 | t=2.267 p<0.05 |
| | Control / Mannitol-Dexamethasone | Mannitol / Dexamethasone |
| Dexamethasone (n:18) 78.42∓7.87 | t=3.981 p<0.01 | t=1.959 p>0.05 |
| | Dexamethasone / Mannitol-Dexamethasone | Mannitol / Mannitol-Dexamethasone |
| Mannitol-Dexamethasone (n:18) 71.10∓12.21 | t=2.138 p<0.05 | t=4.658 p<0.01 |
| Control Group (n:18) 83.05∓4.35 | | |

asing $K^+$ levels significantly, upon comparison to the control group, but mannitol–dexamethasone combination effect in lowering $K^+$ levels was much more significant than their single effect, being $p < 0.05$. (also see Figure–1)

% $H^2O$ *concentrations:* Dexamethasone and mannitol–dexamethasone were not found to have a significant effect in decreasing of $H^2O$ levels on comparison to the control group. But mannitol was alone found to be a highly significant effective in reducing $H^2O$ concentrations as compared to the control group. If we compare 3 treated groups among themselves, Kruskall–Wallis' variance analysis showed again no significant difference (KW: 5.247, df: 2, $\alpha = 0.05$, $p > 0.05$) (Table–3, Figure–1).

Table 3. Comparison of the mean values of % $H_2O$ concentration of cerebellar tissue in the treated and control groups (n: number of rats).

| TREATED GROUPS (with mean values) | COMPARED GROUPS | |
|---|---|---|
| Mannitol (n:18) 75.77∓1.96 | Control / Mannitol | Control / Dexamethasone |
| | t=3.041 p<0.01 | t=1.527 p>0.05 |
| Dexamethasone (n:18) 76.94∓1.35 | Control / Mannitol-Dexamethasone | Mannitol / Dexamethasone |
| | t=1.274 p>0.05 | t=2.085 p<0.05 |
| Mannitol-Dexamethasone (n:18) 77.05∓1.59 | Dexamethasone / Mannitol-Dexamethasone | Mannitol / Mannitol-Dexamethasone |
| | t=0.223 p>0.05 | t=2.151 p<0.05 |
| Control Group (n:18) 77.85∓2.57 | | |

## DISCUSSION

As the pattern of hypoxic–hypoxia brain damage can not be differentiated from the one being secondary to the oligemic–hypoxia, these two types of damages have the same basic pathologic mechanism, which is the inadequate oxygen supply to the neuronal structures (1, 5) that the most sensitive to, in the body (1, 33). Therefore, in either of the pathological condition an aneorobic metabolism of glucose appears, resulting in depletion of the energy stores, cellular acidosis due to excessive lactic acide accumulation within several minutes with an increase in catabolic products and distruption of the normal cell ion homeostasis and finally blood–brain barrier (BBB) is

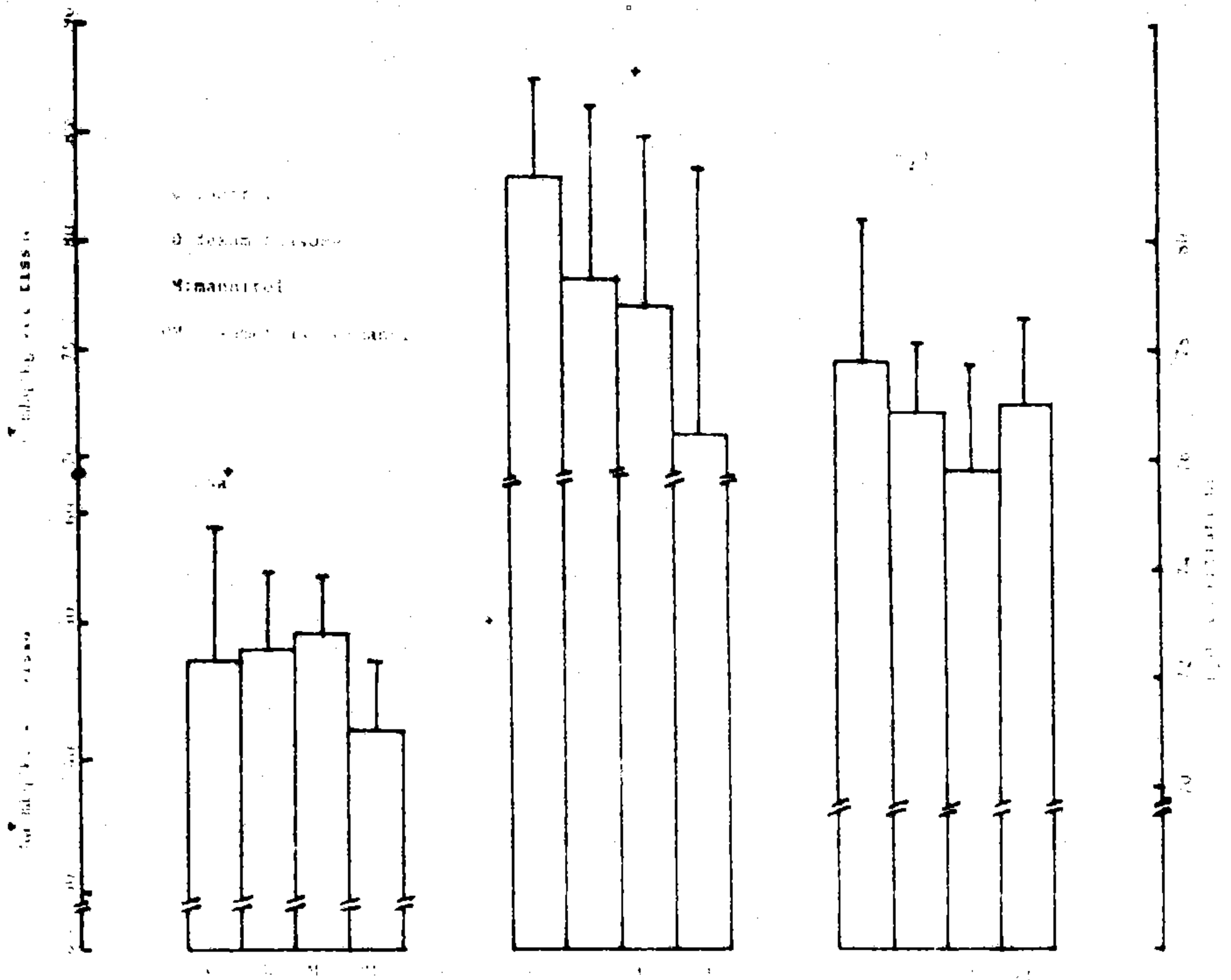

Figure 1. $Na^+$, $K^+$ and $H_2O$ levels are seen, in hypoxic cerebellar tissue.

altered (33, 34). Due to distruption of the cell ion changes, in extracelluler hiperpotasemi and influx of Na and $H^2O$ to intracellular compartment occur; both increased catabolic products and extracellular hiperkalamia are thought to be the main two causes for stimulating astroglial swelling. They show their effect by increasing the metabolic demands and begetting the neuronal tissue more ischemia through distrupting oxygen delivery because of the swell in the elements of the tissue (17). Changes in extracellular ion concentrations causes a loss of potassium and an uptake of sodium into the brain tissue with $H_2O$ (33). Therefore, in the primary phase of the hypoxic–hypoxia or ischemic–hypoxia, CYTOTOXIC, ISCHEMIC EDEMA develops in which the edema fluid usually accumulates intracellularly and then it is followed by neuronal alterations (6, 18, 25). In this experiment, cerebellar swelling was mainly cytotoxic type which was thought on the basis of absent Evans blue staining, but our chemical analysis results were not parallel to EM observations of the cerebellum (11), being most likely secondary to the hypoxia which had a moderate effect on ion changes although it caused neu-

ronal alterations (11). Also, the same controversy between the neuronal and chemical alterations were observed by others (19, 32, 35).

Values of electrolyte and water concentrations are displayed in figure–1 and also compared mean values in the related tables–1 /2 /3 are seen. As mentioned in the study (Part–1) (9), the results of both clinical and experimental studies which mainly related to its effect on reducing of brain swelling (7, 8, 9, 11, 22, 36), maintaining and on improvement of cerebral blood flow (CBF) (7, 8, 21, 26, 36) are contradictory (7, 8, 9, 11, 21, 23. 24, 26, 30, 36, 37).

Steroids are thought to have a beneficial effect by inhibiting the release of arachidonic acid from ischemic cells, if given prior to the onset of ischemia, but the evaluation of its therapy on hypoxic–ischemia or hypoxic–hypoxia brain insults are also both clinically and experimentally are conflicting as well (2, 3, 4, 9, 10, 11, 12, 13, 14, 16, 20, 27, 28, 29, 31).

Conclusion of this experimental study in hypoxic cerebellar tissue was contradictive as well, in which, mannitol was in the first rank in effecting $H_2O$ contents, dexamethasone in second and combination of them in third ranks if compared each other.

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