Scientific Research Publishing

Open Journal of Emergency Medicine, 2017, 5, 102-109
http://www.scirp.org/journal/ojem
ISSN Online: 2332-1814
ISSN Print: 2332-1806

Bromocriptine in Central Hyperthermia after Severe Traumatic Brain Injury

Tamer Zakhary[1*], Ahmed Sabry[2]

[1]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[2]Department of Neurosurgery, Faculty of Medicine, Alexandria University, Alexandria, Egypt
Email: *Tamer_zakhary@hotmail.com

How to cite this paper: Zakhary, T. and Sabry, A. (2017) Bromocriptine in Central Hyperthermia after Severe Traumatic Brain Injury. *Open Journal of Emergency Medicine*, **5**, 102-109.
https://doi.org/10.4236/ojem.2017.53010

Received: August 4, 2017
Accepted: September 12, 2017
Published: September 15, 2017

Abstract

Strong evidence showed that fever after traumatic brain injury TBI is associated with increased mortality. In this study, we tried to evaluate the role of Bromocriptine in central hyperthermia in patients with severe TBI. This prospective controlled study was conducted on 50 severe TBI patients who admitted to the critical care department and confirmed on Computed Tomography (CT) of the brain and GCS of less than 9 at admission. Then, they were randomly assigned into 2 groups. Bromocriptine group (25) received bromocriptine 7.5 mg/day during 24 hours from admission through a naso-gastric (NG) feeding tube. Control group (25) received conventional treatment only. Temperature was measured every 2 hours. The antipyretic measures used were the same across all patients enrolled. The primary outcome was number of patients diagnosed with central hyperthermia. After the discharge of all patients, there was a statistically significant difference between the 2 groups in number of patients diagnosed with central hyperthermia (6 (24%) in bromocriptine group Vs 18 (72%) in control, $p = 0.002$). There were no differences in hospital length of stay ($p = 0.904$) or mortality ($p = 0.393$). Early administration of bromocriptine in severe TBI may be associated with lower incidence of central hyperthermia with no effect on length of stay or mortality.

Keywords

Critical, Neurology, Traumatic Brain Injury, Central Hyperthermia, Bromocriptine

1. Introduction

Traumatic brain injury (TBI) is structural injury and/or physiologic disruption of brain function from blunt trauma, acceleration or deceleration forces, or ex-

posure to blast [1]. Severe TBI is usually defined with a Glasgow coma score (GCS) of ≤8 within the first two days following trauma [2]. Hyperthermia is a common symptom among critically ill patients. Generally, hyperthermia is more related to infectious diseases [3] [4]. One study in an intensive care unit (ICU) setting revealed that 70% of admissions were febrile at some point during their hospital stay [5]. Hyperthermia after TBI is associated with poor diagnosis [6] [7]. It is associated with marked fluctuations in body temperature and a rapid response [8].

The pathophysiology of central hypothermia is usually originated from a dysfunction in central fever control centers as the level of the diencephalon [9] [10]. This area regulates the core temperatures. Two studies showed that any damage can disrupt the thermoregulatory apparatus of the body [10]. In 1940, it was reported that central fever would develop in humans sustaining damage to the hypothalamus during neurosurgery [11] [12]. A lot of theories demonstrated the relation between the hypothalamus and central hyperthermia [9] [10] [13] [14]. It may be related the selective loss of warm-sensitive neurons, progesterone or prostaglandin hormonal changes leading to modification in the firing rate of heat sensitive neurons in the medial preoptic nucleus (MPO) or osmotic changes detected by organum vasculosum laminae terminalis (OVLT) [13].

There is evidence that fever is common in patients with acute TBI [15] [16]. It has also been suggested that fever may be beneficial in general medical population against infections, and aggressive fever reduction may not be indicated [14] [17]. Strong evidence showed that fever after brain injury is associated with increased mortality [17] [18] [19] [20] [21]. Mortality was observed to be higher in patients with TBI and stroke with early fevers but not in CNS infections [19].

Bromocriptine is an ergot-derivative dopamine D2 receptor agonist and prolactin inhibitor [22]. It has well known off label use to relieve hyperthermia, extrapyramidal reactions and hypertension of neuroleptic malignant syndrome associated with neuroleptic drug therapy [23]. There is an increasing evidence showing that central fever is associated with poor response to traditional antipyretics [24]. So, it may require a multimodal approach of management with new medications as Bromocriptine and/or surface or intravascular cooling device [25]. In this study, we tried to evaluate the role of Bromocriptine in central hyperthermia in patients with severe TBI.

2. Methods

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria University and the department of critical care, informed consent was taken from the next of kin. This prospective controlled study was conducted on severe TBI patients who admitted to the critical care department and confirmed on Computed Tomography (CT) of the brain and GCS of less than 9 at admission. Randomly selected patients were enrolled if they were adults of both sexes (except pregnant females). Exclusion criteria in-

cluded the following; any patient with non-survivable TBI (head Abbreviated Injury Score-Code = 6), pure surgical lesions, significant polytrauma, traumatic spinal cord injuries, dysautonomia, cardiovascular instability, electrolyte imbalance, coagulopathy, uncontrolled hypertension, chest trauma and active seizures.

All enrolled patients were assessed at the time of admission, the following parameters were documented at enrollment: Personal data, Complete clinical examination including Glasgow coma scale (GCS), regional abbreviated injury scale (AIS) score, Injury Severity Score (ISS), blood pressure (B.p), temperature (T), heart rate, respiratory rate (RR). Marshall CT classification and Rotterdam CT score were calculated after the 1st CT of the brain.

All enrolled patients who completed the study (n = 50) were randomly assigned into two groups. Bromocriptine group [25] received bromocriptine 7.5 mg/day during 24 hours from admission through a naso-gastric (NG) feeding tube, then changed to oral route after good swallowing and gag reflex were ensured. Bromocriptine was held if patient developed any contraindication to it. Control group [25] received conventional treatment only without bromocriptine.

All routine laboratory investigations were followed up including complete blood count (CBC), serum electrolytes, serum creatinine (mg/dl), serum urea (mg/dl), random blood sugar (mg/dl), alanine aminotransferase (U/L), aspartate aminotransferase (U/L), total bilirubin (mg/dl). Also, a standard 12 lead electrocardiogram "ECG" was done for all enrolled patients.

All patients were followed up during their ICU stay. GCS was measured every 12 hours; vital signs including mean arterial pressure, pulse rate and respiratory rate were measured every 4 hours. Temperature was measured every 2 hours. The antipyretic measures used were the same across all patients enrolled. All episodes of fever during hospital stay were assessed according to following protocol (**Figure 1**) [26]. The primary outcome was number of patients diagnosed with central hyperthermia during their hospital stay. The secondary outcomes were hospital length of stay in days and mortality.

Statistical Analysis

Data were collected onto an electronic spreadsheet and Statistical Package (Version 24, SPSS) was used for statistical analyses. Descriptive statistics were reported as raw percentages or means and standard deviations. A Student's t-test or Mann-Whitney test was used when appropriate to compare means for parametric or non-parametric data respectively. A chi-square test or Fisher's exact test was performed for comparison of categorical variables. $p < 0.05$ was considered statistically significant.

3. Results

Regarding the basic characteristic features of patients enrolled, 33 patients were males and only 17 were females. No cases were withdrawn from the study because

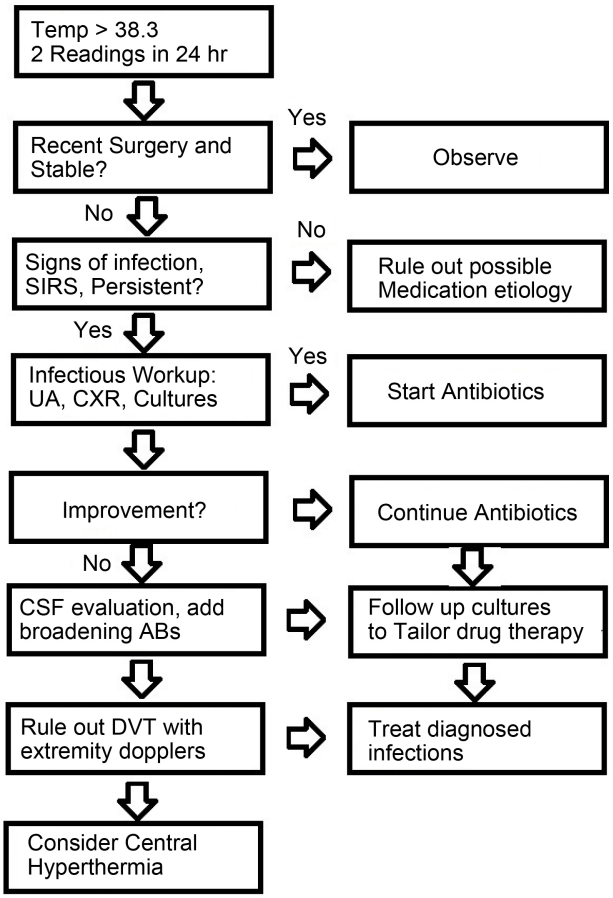

Figure 1. Fever workup algorithm [26].

of adverse reactions of the drug. The mean age of all patients was about 41 years. There were no any statistically significant differences between the two studied groups in their demographics like age and sex. All vital signs between the two groups were nearly the same. The mean GCS in the control group was slightly lower than the mean in bromocriptine group but without significant difference (4.99 Vs 5.12, $p = 0.604$ respectively) (**Table 1**). All baseline laboratory data, AIS score, Marshall CT classification and Rotterdam CT score were nearly the same between the 2 groups.

After hospital discharge of all patients, the study main outcomes were calculated. About half of all studied patients (n = 50) were diagnosed with central hyperthermia during their hospital stay. 18 of them were control patients while only 6 were patients of bromocriptine group. There was a statistically significant difference between the 2 groups in number of patients diagnosed with central hyperthermia (6 (24%) in bromocriptine group Vs 18 (72%) in control, $p = 0.002$). The mean of all patient's length of stay was 33.02 days. There was no significant difference between the 2 groups in their mean of hospital length of stay ($p = 0.904$). Although mortality rate in control group was higher, there was no a statistically significant difference between the two groups in number of survived patients (13 in bromocriptine group while 9 in control, $p = 0.393$) (**Table 2**).

Table 1. The basic characteristic features of the two studied groups at admission.

	Bromocriptine (n = 25)	Control (n = 25)	*p value*
Age (years) Mean ± S.D.	40.41 ± 10.96	41.60 ± 8.10	0.961
Sex Female Male	 9 (36%) 16 (64%)	 8 (32%) 17 (68%)	0.771
HR (beats/min) Mean ± S.D.	98.36 ± 10.35	105.29 ± 7.73	0.901
SBP (mmHg) Mean ± S.D.	130.40 ± 18.24	120.18 ± 20.11	0.759
GCS Mean ± S.D.	5.12 ± 1.89	4.99 ± 1.07	0.604
Temp. (˚C) Mean ± S.D.	37.6 ± 1.18	37.9 ± 0.29	0.401

HR: Heart rate, SBP: Systolic blood pressure, GCS: Glasgow coma scale, Temp: Temperature. P values for student t test. P is significant if <0.05.

Table 2. The measured outcomes in the two studied groups.

	Bromocriptine (n = 25)	Control (n = 25)	*p value*
Patients Diagnosed with Central Hyperthermia (no, %)	6 (24%)	18 (72%)	0.002**
Hospital Length of stay (days) Mean ± S.D.	33.40 ± 19.028	32.64 ± 24.708	0.904
All cause In-hospital Mortality Survived (no, %)	13 (52%)	9 (36%)	0.393

p values for Fisher's exact and Mann Whitney tests. **p is significant if < 0.05.

4. Discussion

Central fever can occur alone or in conjunction with other autonomic and motor findings [27]. These are known as paroxysmal sympathetic hyperactivity (PSH). Hyperthermia of central origin has a rapid onset and marked fluctuation with poor response to usual antipyretics [24]. In a study of 74 patients with post stroke central hyperthermia, nearly 70% of the patients with fever expired within one month, especially those with temperatures >39˚C [8]. The characteristics of central hyperthermia may be due to the compression of hypothalamic and brainstem thermoregulatory centers [28].

Bromocriptine is a dopamine (D2) agonist. It acts on the corpus striatum and the hypothalamus [29]. It may help in PSH, due to its action on dopaminergic transmission [30] [31]. Unfortunately, there is no a lot of studies on the efficacy of bromocriptine in traumatic brain injury [32]. All evidences are only case reports and small studies [32]. In a recent study, bromocriptine was found to improve neurological sequelae of TBI and the overall outcome in the patients. but

central hyperthermia was not assessed in the trial [33].

In another study, bromocriptine showed positive consequences on traumatic brain injury-induced cognitive deficits [34]. In our trial we studied the relation between early bromocriptine administration after severe traumatic brain injury and the incidence of central hyperthermia. Bromocriptine showed 48% less incidence of central hyperthermia ($p = 0.002$). There were no differences between the 2 groups in hospital stay or mortality. It may be due to the small sample size studied.

5. Conclusion

Early administration of 7.5 mg/day bromocriptine in adult patients with severe traumatic brain injury may be associated with lower incidence of central hyperthermia with no effect on other outcomes like length of stay or mortality. Limitations of this study were small sample size and using the same dose for all patients. Further studies should individualize the therapy for each patient and evaluate the improvement in temperature management in patients treated with bromocriptine in the setting of central hyperthermia.

6. Ethics

After ethical approval for this clinical trial from the local committee of ethics in the faculty of medicine of Alexandria University and the department of critical care medicine, Informed consents for participating and publishing were taken from the next of kin of patients after approval by critical care department committee.

Availability of Data and Materials

Please contact author for any data requests.

Competing Interests

The author declares that there are no competing interests.

References

[1] VA/DoD (2009) Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. *Journal of Rehabilitation Research and Development*, **46**, 1-68. https://doi.org/10.1682/JRRD.2008.03.0038

[2] Teasdale, G. and Jennett, B. (1974) Assessment of Coma and Impaired Consciousness: A Practical Scale. *The Lancet*, **304**, 81-84. https://doi.org/10.1016/S0140-6736(74)91639-0

[3] Georgilis, K., Plomaritoglou, A., Dafni, U., Bassiakos, Y. and Vemmos, K. (1999) Aetiology of Fever in Patients with Acute Stroke. *Journal of Internal Medicine*, **246**, 203-209. https://doi.org/10.1046/j.1365-2796.1999.00539.x

[4] Roth, E.J., Love, L.L.L., Harvey, R.L., Heinemann, A.W., Semik, P. and Diaz, S. (2001) Incidence of and Risk Factors for Medical Complications during Stroke Rehabilitation. *Stroke*, **32**, 523-529. https://doi.org/10.1161/01.STR.32.2.523

[5] Circiumaru, B., Baldock, G. and Cohen, J.A. (1999) Prospective Study of Fever in the Intensive Care Unit. *Intensive Care Medicine*, **25**, 668-673. https://doi.org/10.1007/s001340050928

[6] Lakhan, S.E. and Pamplona, F. (2012) Application of Mild Therapeutic Hypothermia on Stroke: A Systematic Review and Meta-Analysis. *Stroke Research and Treatment*, 2012, Article ID: 295906. https://doi.org/10.1155/2012/295906

[7] Castillo, J., Dávalos, A., Marrugat, J. and Noya, M. (1998) Timing for Fever-Related Brain Damage in Acute Ischemic Stroke. *Stroke*, **29**, 2455-2460. https://doi.org/10.1161/01.STR.29.12.2455

[8] Sung, C.Y., Lee, T.H. and Chu, N.S. (2009) Central Hyperthermia in Acute Stroke. *European Neurology*, **62**, 86-92. https://doi.org/10.1159/000222778

[9] Saper, C.B., Lu, J., Chou, T.C. and Gooley, J. (2005) The Hypothalamic Integrator for Circadian Rhythms. *Trends in Neurosciences*, **28**, 152-157. https://doi.org/10.1016/j.tins.2004.12.009

[10] Crompton, M.R. (1971) Hypothalamic Lesions Following Closed Head Injury. *Brain*, **94**, 165-172. https://doi.org/10.1093/brain/94.1.165

[11] Zimmerman, H. (1940) Temperature Disturbances and the Hypothalamus. *Research Publications—Association for Research in Nervous and Mental Disease*, **20**, 824-840.

[12] Davison, C. (1940) Disturbances of Temperature Regulation in Man. *Research Publications—Association for Research in Nervous and Mental Disease*, **20**, 774-823.

[13] Rango, M., Arighi, A., Airaghi, L. and Bresolin, N. (2012) Central Hyperthermia, Brain Hyperthermia and Low Hypothalamus Temperature. *Clinical Autonomic Research*, **22**, 299-301. https://doi.org/10.1007/s10286-012-0174-6

[14] Bernheim, H., Block, L. and Atkins, E. (1979) Fever: Pathogenesis, Pathophysiology, and Purpose. *Annals of Internal Medicine*, **91**, 261-270. https://doi.org/10.7326/0003-4819-91-2-261

[15] Badjatia, N. (2009) Fever Control in the Neuro-ICU: Why, Who, and When? *Current Opinion in Critical Care*, **15**, 79-82. https://doi.org/10.1097/MCC.0b013e32832922e9

[16] Rincon, F., Patel, U., Schorr, C., Lee, E., Ross, S., Dellinger, R.P., *et al.* (2015) Brain Injury as a Risk Factor for Fever upon Admission to the Intensive Care Unit and Association with In-Hospital Case Fatality: A Matched Cohort Study. *Journal of Intensive Care Medicine*, **30**, 107-114. https://doi.org/10.1177/0885066613508266

[17] Moltz, H. (1993) Fever: Causes and Consequences. *Neuroscience & Biobehavioral Reviews*, **17**, 237-269.

[18] Fernandez, A., Schmidt, J., Claassen, J., Pavlicova, M., Huddleston, D., Kreiter, K., *et al.* (2007) Fever after Subarachnoid Hemorrhage Risk Factors and Impact on Outcome. *Neurology*, **68**, 1013-1019. https://doi.org/10.1212/01.wnl.0000258543.45879.f5

[19] Saxena, M., Young, P., Pilcher, D., Bailey, M., Harrison, D., Bellomo, R., *et al.* (2015) Early Temperature and Mortality in Critically Ill Patients with Acute Neurological Diseases: Trauma and Stroke Differ from Infection. *Intensive Care Medicine*, **41**, 823-832. https://doi.org/10.1007/s00134-015-3676-6

[20] Diringer, M.N., Reaven, N.L., Funk, S.E. and Uman, G.C. (2004) Elevated Body Temperature Independently Contributes to Increased Length of Stay in Neurologic Intensive Care Unit Patients. *Critical Care Medicine*, **32**, 1489-1495. https://doi.org/10.1097/01.CCM.0000129484.61912.84

[21] Greer, D.M., Funk, S.E., Reaven, N.L., Ouzounelli, M. and Uman, G.C. (2008) Impact of Fever on Outcome in Patients with Stroke and Neurologic Injury. *Stroke*, **39**, 3029-3035. https://doi.org/10.1161/STROKEAHA.108.521583

[22] Olanow, C.W. and Koller, W.C. (1998) An Algorithm (Decision Tree) for Themanagement of Parkinson's Disease Treatment Guidelines. *Neurology*, **50**, S1-S88.

[23] McEvoy, G.K. (2000) AHFS Drug Information. American Society of Health-System Pharmacists.

[24] Yu, K.-W., Huang, Y.-H., Lin, C.-L., Hong, C.-Z. and Chou, L.-W. (2013) Effectively Managing Intractable Central Hyperthermia in a Stroke Patient by Bromocriptine: A Case Report. *Neuropsychiatric Disease and Treatment*, **9**, 605.

[25] Samudra, N. and Figueroa, S. (2016) Intractable Central Hyperthermia in the Setting of Brainstem Hemorrhage. *Therapeutic Hypothermia and Temperature Management*, **6**, 98-101. https://doi.org/10.1089/ther.2016.0004

[26] Meier, K. and Lee, K. (2017) Neurogenic Fever: Review of Pathophysiology, Evaluation, and Management. *Journal of Intensive Care Medicine*, **32**, 124-129. https://doi.org/10.1177/0885066615625194

[27] Rabinstein, A.A. (2007) Paroxysmal Sympathetic Hyperactivity in the Neurological Intensive Care Unit. *Neurological Research*, **29**, 680-682. https://doi.org/10.1179/016164107X240071

[28] Deogaonkar, A., De Georgia, M., Bae, C., Abou-Chebl, A. and Andrefsky, J. (2005) Fever Is Associated with Third Ventricular Shift after Intracerebral Hemorrhage: Pathophysiologic Implications. *Neurology India*, **53**, 202. https://doi.org/10.4103/0028-3886.16411

[29] Kang, S.H., Kim, M.J., Shin, I.Y., Park, D.W., Sohn, J.W. and Yoon, Y.K. (2012) Bromocriptine for Control of Hyperthermia in a Patient with Mixed Autonomic Hyperactivity after Neurosurgery: A Case Report. *Journal of Korean Medical Science*, **27**, 965-968. https://doi.org/10.3346/jkms.2012.27.8.965

[30] Russo, R. and O'Flaherty, S. (2000) Bromocriptine for the Management of Autonomic Dysfunction after Severe Traumatic Brain Injury. *Journal of Paediatrics and Child Health*, **36**, 283-285. https://doi.org/10.1046/j.1440-1754.2000.00485.x

[31] Bullard, D.E. (1987) Diencephalic Seizures: Responsiveness to Bromocriptine and Morphine. *Annals of Neurology*, **21**, 609-611. https://doi.org/10.1002/ana.410210617

[32] Frenette, A.J., Kanji, S., Rees, L., Williamson, D.R., Perreault, M.M., Turgeon, A.F., *et al.* (2012) Efficacy and Safety of Dopamine Agonists in Traumatic Brain Injury: A Systematic Review of Randomized Controlled Trials. *Journal of Neurotrauma*, **29**, 1-18. https://doi.org/10.1089/neu.2011.1812

[33] Munakomi, S., Bhattarai, B. and Mohan Kumar, B. (2017) Role of Bromocriptine in Multi-Spectral Manifestations of Traumatic Brain Injury. *Chinese Journal of Traumatology*, **20**, 84-86.

[34] Phelps, T.I., Bondi, C.O., Ahmed, R.H., Olugbade, Y.T. and Kline, A.E. (2015) Divergent Long-Term Consequences of Chronic Treatment with Haloperidol, Risperidone, and Bromocriptine on Traumatic Brain Injury-Induced Cognitive Deficits. *Journal of Neurotrauma*, **32**, 590-597. https://doi.org/10.1089/neu.2014.3711