Available online on 15.04.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

Non-Selective Beta-Adrenergic Blocker Propranolol: A Life Saving Drug for Hospitalized Patient with Traumatic Brain Injury in Intensive Care Unit

Ashwathi P[1]*, Srinivas K[2]

[1] *Doctor of Pharmacy, Department of Clinical Pharmacy, Neurofoundation Hospital, 3 roads-636009, Tamil Nadu, India*

[2] *Doctor of Pharmacy, Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India*

Article Info:

Article History:

Received 12 Feb 2023
Reviewed 16 March 2023
Accepted 29 March 2023
Published 15 April 2023

Cite this article as:

Ashwathi P, Srinivas K, Non-Selective Beta-Adrenergic Blocker Propranolol: A Life Saving Drug for Hospitalized Patient with Traumatic Brain Injury in Intensive Care Unit, Journal of Drug Delivery and Therapeutics. 2023; 13(4):145-148

DOI: http://dx.doi.org/10.22270/jddt.v13i4.6025

*Address for Correspondence:

Dr. P. Ashwathi, Clinical Pharmacist, Department of Clinical Pharmacy, Neurofoundation Hospital, 3-roads, Salem-636009, Tamilnadu, India.

Abstract

Background: Traumatic Brain Injury (TBI) is the most common cause of death under the age of forty. This in turn results in intracranial injury in about 90% of the cases from least-income countries. The majority of patients admitted to the Intensive care Unit (ICU) had trauma which is managed by preventive strategies and to combat the secondary hit stimulated by the primary hit International guidelines have formed a protocol to be applied in patients with TBI for the better outcome and to increase the survival rate.

Objectives: The aim of this study was to determine the importance of beta-adrenergic blocker propranolol in patients admitted with TBI.

Methodology: The literature search was conducted to find recent articles related to the aim of the study to analyze the significance of beta-blocking agent propranolol in TBI.

Results: Paroxysmal Sympathetic Hyperactivity (PSH) occurs within 24 hours of TBI in patients with Glasgow Coma Scale (GCS ≤ 8). In patients who are agitated or in restlessness propranolol is the drug of choice to reduce hyperactivity. Several studies reported that using beta-adrenergic blocking agents decreases the mortality rate and current studies started focusing on the primary initiation of propranolol and also reported side-effects associated in TBI.

Conclusion: Early administration of Non-selective beta-adrenergic blocker propranolol will continue to be the standard prophylactic pharmacotherapeutic method as it limits the risk of sympathetic storming in high-risk patients with TBI.

Keywords: Traumatic Brain Injury (TBI), Propranolol, Beta-adrenergic blocker, Paroxysmal Sympathetic Hyperactivity (PSH).

1. INTRODUCTION

Traumatic Brain Injury in Intensive Care Unit

One of the most tremendous causes of mortality worldwide is due to Traumatic brain injury (TBI) commonly in people under the age of forty [1]. All most every case related to trauma results in intracranial harm to the individuals. It is estimated that about 90% of the deaths are from defective income countries[2].In Patients with severe TBI, it often resulted in a major neurological outcome where trauma is the primary hit which is managed by preventive strategies and the second hit occurs from the complication of primary insult which is accompanied by cerebral edema, ischemia, and hypoxia. It is believed that secondary insult may aggravate the condition through cerebral vasoconstriction and ischemia by adrenergic cyclones induced by primary insult [3, 4]. To combat these two traumatic factors international guidelines have made a protocol for better outcomes for traumatized patients through standard management in the intensive care unit (ICU). This is composed of standardized neurointensive care, Neurosurgical interventions, neuro-specific monitoring and, the use of intracranial pressure monitoring [5, 6]. Several researchers started focusing on reducing the prevalence of secondary brain injury mainly to improve the quality of life in TBI patients and also few studies from both prospective as well as retrospective data reported that the early use of beta-blockers shows promising results in managing the sympathetic storms[7-10].

Sympathetic Storming in Patients with Traumatic Brain Injury

In the ICU patients with moderate to severe TBI associated with restlessness and agitation are frequently sedated and incubated in order to reduce the workload of the brain. This hyperactive response is called sympathetic storming which occurs in the comatose of Glasgow Coma Scale (GCS ≤ 8) within 24 hours of brain injury or weeks later [11, 12]. The cause of sympathetic storming is because of acceleration in sympathetic nervous system activity in charge of the parasympathetic activity in the central nervous system which results in loss of cortical control due to downregulation of autonomic balance in the brain injury [13]. Where specific alpha-1, alpha-2, beta 1, and beta 2 adrenergic receptors are disturbed which results in response to individual target organs [14]. To understand this condition signs and symptoms should take place back-to-back with a minimum of 1 cycle per day [15]. Heart rate, blood pressure, respiratory rate,

temperature, sweating, posturing, and laboratory details are accompanied in TBI patients once the sedatives and narcotics are discontinued in the ICU and this helps us to identify the elevated serum catecholamine in hospitalized patients with TBI [16-19].

Role of Non-Selective beta-blocker Propranolol in Traumatic Brain Injury

A Non-Selective beta-adrenergic antagonist propranolol, is one of the most customarily used treatments in the case of paroxysmal sympathetic hyperactivity (PSH) to balance the secondary complications. It acts on two types of beta-adrenergic receptors (beta-1 and beta-2) where, beta-1are located in the heart, brain, and kidney and beta -2 in the liver, lungs, skeletal muscles, arterioles, and eyes [20]. It has both cardioprotective and neuroprotective effects thereby exerting its action through decreasing the heart rate, stroke volume, and arterial pressure as well as lowering the cerebral blood flow, oxygen, and glucose accumulation by reducing the cerebral metabolism [21]. Compared to cardio-selective beta-adrenergic blockers, propranolol has the huge advantage in that it has a lipophilic property that can easily penetrate into the blood brain barrier (BBB) and mediates central action by controlling theparoxysms[22-24]. As a result, an increase in catecholamines activates an inflammatory process which is harmful in patients with TBI. Implementation of empirical administration of beta-blocking agents within 24 hours of brain injury will decrease sympathetic storming and enhance the patient's quality of life [25]. The aim of this review is to study and analyze the initial use of beta-adrenergic blocking agent propranolol which is used as a lifesaving drug in patients with TBI in various experimental studies.

2. METHODOLOGY

The information was collected from various articles through online search tools like PubMed, Embase, Scopus, and Medline by applying the key formula ("Traumatic Brain Injury" OR "sympathetic storming") and ("Propranolol" OR "Beta blocking agent In Traumatic Brain Injury" OR" "paroxysmal sympathetic hyperactivity") and ("Randomized control trials" OR " Prospective studies" OR "Retrospective studies") and contents were extracted from the identified articles and correlated according to the need of the study.

3. RESULTS AND DISCUSSION:

1.1 The Outcome and effectiveness of propranolol in TBI

At present, there are several human as well as animal studies on adrenergic agonists/antagonists as the treatment option in patients with TBI and it has been reported that using both drug classes has a protective action against secondary complications[26]. This is because of the certainty that through negative feedback action, agonistic drug manages the receptor pursuit[27-29] and it upregulates beta-2 adrenergic receptors after the TBI[30]. Current studies mainly focus on the primary utilization of beta-adrenergic blocking agents and their outcome measures in patients admitted with TBI.

A prospective randomized control trial was conducted by (Hosseinali Khalili et al) [31] for the span of eight months in patients with severe TBI. This study was carried out to evaluate the effective outcome of beta-adrenergic blockers in TBI. Around 356 patients were assessed for eligibility out of them 222 were randomized based on inclusion and exclusion criteria of which 18 were declined from the trial and 102 patients were allotted equally to each group. In the intervention arm three of them lost follow-up due to bradycardia and only 99 were taken for analysis in the control arm all 102 were included as they were on continuous duplicate intervention. During the treatment period due to severe extracranial injury, 31 were excluded from the intervention group and 34 from the no-intervention group. Finally, 68(Intervention) and 86 (No Intervention) were in follow-up at the end of the study.

As a result, 18.6% were declared from the no-intervention group compared to the intervention group with a mortality rate of 4.4% in the isolated TBI. From this randomized trial it was concluded that early use of beta-adrenergic blocker propranolol 20mg every 12 hours orally will improve the existence rate and outcome in patients with severe TBI for the period of six months from the time of injury.

Similarly, the trial conducted by (Ammar and Hussein) [32] was a double-blinded study in which 30 patients (Group A) was undergone treatment with propranolol and the remaining 30 patients (Group B) received a placebo. In the study discussed previously which was undertaken by (Hosseinali Khalili et al)[31]Non-Selective beta-adrenergic blocker Propranolol was given as oral therapy but, in this clinical trial propranolol 1mg was given intravenously within 24 hours of TBI and it was followed for one week every 6 hourlies. The aim of this trial was to analyze the improvement in the elevated serum catecholamines that occur in TBI. From this study it was observed that empirical use of propranolol has reduced serum catecholamine levels in Group A compared to Group B on day seven further, it also improved GCS in the propranolol group and it exhibited statistically significant variation compared to Group B. Comparing the results from the above observational study this clinical trial data clearly shows that the long-term clinical outcome and the mortality rate was not recorded.

1.2 Lund's concept on the administration of beta-blocker in TBI

The Empirical administration of beta-blocker propranolol and whether it has to be included in the standardized treatment protocol in patients with TBI is still debated in the neuro-intensive care unit (NICU)[6]. According to Brain Trauma Foundation, this therapy is not specifically advised whereas, in Lund's concept administration of propranolol is recommended to manage brain capacity, O2, and perfusion by controlling the systemic blood pressure (SBP). In addition, extracranial effects induced by TBI are also alleviated with the help of beta-blockade by lowering the sympathetic storming and accumulation of fluids resulting in the devastation of BBB. Various protocols have been formulated from both retrospective as well as animal studies but, none of them introduced Lund's concept in randomized control trials (RCT). Even though, nowadays this concept is vastly used in huge countries in order to analyze the risks and benefits of the administration of propranolol[20].

Several groups from Lund's concept developed the following cardinal steps to achieve the targeted outcome.1) Lowering the stress by blocking the catecholamines and proving adequate sedation; 2) maintaining normal fluid balance; 3) to maintain cerebral perfusion pressure; 4) restricting cerebral drainage; 5) promoting the adequate use of oxygen and ventilation and 6) early use of nutrition[33-35]. To accentuate this, one study used a selective beta-1 blocker, metoprolol to minimize the myocardial contraction as well as an alpha-2 agonist, clonidine to inhibit the catecholamine and produce vasodilatory action. The combined effect of the drugs showed a decrease in hydrostatic pressure and an increase in reabsorption[36, 37]. The other study identified that the use of propranolol in TBI minimized the risk of death rate with an odds ratio: of 0.54 also, it increased the survival rate in patients with raised cardiac troponins. While differentiating the type of beta-blockers it was observed that non-selective beta-adrenergic blocker propranolol showed reduced

mortality and better outcome compared to specific beta-selective blockers[38].

1.3 Risks associated with beta-adrenergic blocker in TBI

The only thing that bothered the clinical trial was the side effects associated with patients undergoing treatment with propranolol. The first one is hypotensive incidents and the second concern is bronchoconstriction-induced hypoxia due to the blockade of beta-2 adrenergic blocker and this increases the risk of mortality[39]. One study reported that no such events had occurred in patients with TBI in the intervention group compared to the control group[40] and also it has been noted that safety measures and considerations were taken for prudent administration of beta-blockers in a sequence of such adverse drug events by Cruickshank and colleagues[41].Fascinatingly, in the trial conducted by (Hosseinali Khalili et al)[31] no such hypotensive or hypoxic events had been reported but, only three patients lost follow-up due to lowering heart rate and theysettled with good response at the time of discharge.

On the other side, the case reported by (Mayank Garg et al)[42]on neurogenic fever (NF) in TBI patients who had undergone treatment with propranolol. NF is usual in Severe TBI and various studies have reported an occurrence rate of 4 to 37 % due to the disruption of temperature points in the hypothalamus.[43,44] A twenty- six-year-old male admitted with complaints of a road traffic accident (RTA) with multiple contusions where taken for a decompressive carniectomy. After his post-operation, he developed a fever and was on supportive treatment with antibiotics and paracetamol. Even though, his temperature was not declined and started propranolol 10mg BID on the seventh day of post-operation assuming it was an NF. On the day-17 of his post-operation, he developed hypothermia. Unexpectedly, the temperature returned to normal on the very next day the drug was stopped. This study concludes that stopping propranolol earlier has helped them to maintain the normal temperature in patients with TBI and it also suggests that future studies must focus on when to stop the drug therapy.

4. CONCLUSION

In general it is known that sympathetic storming is common in patients with TBI admitted to the ICU. The main intension is to rapidly stop the adrenergic cyclones stimulated by the primary complications during the TBI. Various preclinical and clinical studies in the year of 2020 had taken multiple steps to improve the therapeutic outcome but, there is a lack in understanding the modern pathophysiological changes, recognition methods, clinical findings, and interventions which is mandatory to achieve the targeted therapy and this gap has to be kept in consideration for the further clinical trials. The recent studies suggest that using beta-adrenergic blocker propranolol in the hospitalized patients with TBI decreases the elevated catecholamines as well as increases the survival rate. This review concludes from the identified articles that, initial administration of Non-selective beta-adrenergic blocker propranolol is the drug of choice and will continue to be the standard prophylactic pharmacotherapeutic interventions as it reduces the risk of PSH in patients with TBI as well as improves GCS and further RCT are required to evaluate the safety, efficacy, duration of propranolol therapy and impression of these hopeful interventions to improve the quality of life and better clinical outcome following TBI.

Conflicts of Interest: Authors declare that they have no conflicts of interest.

Funding statement: This review did not receive any funding.

REFERENCES:

1. Corrigan JD, Selassie AW, Orman JA, etal.The epidemiology of traumatic brain injury. J Head Trauma Rehabil. 2010; 25(2):72-80. https://doi.org/10.1097/HTR.0b013e3181ccc8b4

2. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018; 1-18.10.3171/2017.10. JNS17352

3. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma.1993; 34:216-222. https://doi.org/10.1097/00005373-199302000-00006

4. Manley G, Knudson MM, MorabitoD, et al. Hypotension, hypoxia, and head injury: frequency, duration and consequences. Arch Surg. 2001; 136(10):1118-1123. https://doi.org/10.1001/archsurg.136.10.1118

5. CarneyN, et al. Guidelines for management of severe TBI, 4th edn.Available at: https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf.(accessed 11May 2017).

6. Koskinen LOD, Olivecrona M, Grande PO, et al. Severe traumatic brain injury management and clinical outcome using the Lund concept. Neuroscience. 2014; 283:245-255. https://doi.org/10.1016/j.neuroscience.2014.06.039

7. Alali AS, McCredie VA, Golan E, et al. Beta blockers for acute traumatic brain injury: a systematic review and metaanalysis. Neurocrit Care. 2014; 20:514. https://doi.org/10.1007/s12028-013-9903-5

8. Cotton BA, Snodgrass KB, Fleming SB, et al. Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. J Trauma Injury Infect Crit Care.2007; 62(1):26-35. https://doi.org/10.1097/TA.0b013e31802d02d0

9. Ko A, Harada MY, Barmparas G, et al. Early propranolol after traumatic brain injury is associated with lower mortality. J Trauma Acute Care Surg.2016; 80(4):637-642. https://doi.org/10.1097/TA.0000000000000959

10. Dhillon NK, Inaba K, Salim A, et al. Beta blockers in critically ill patients with traumatic brain injury: results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. J Trauma Acute Care Surg. 2018; 84(2):234-244. https://doi.org/10.1097/TA.0000000000001747

11. Mohseni S, Talving P, Wallin G, et al. Pre-injury betablockade is protective in isolated severe traumatic brain injury. J Trauma. 2014; 76(3):804-808. https://doi.org/10.1097/TA.0000000000000139

12. Kishner S, Augustin J, Strum S, et al. Post headinjury autonomic complications. Availableat: www.emedicine.com/pmr/topic108.htm.(accessed 8 November 2006).

13. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL,Chestnut RM, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma. 2007; 24 (1): S7-13.10.1089/neu.2007.9995

14. Arbabi S, Campion EM, Hemmila MR, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma.2007; 62:56-61. https://doi.org/10.1097/TA.0b013e31802d972b

15. Perkess I, Baguley IJ, Nott MT, M, et al. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol.2010; 68:126-35. https://doi.org/10.1002/ana.22066

16. Baguley IJ, Cameron ID, Green AM, et al. Pharmacological management of dysautonomia following traumatic brain injury. Brain Inj. 2004; 18:409-417. https://doi.org/10.1080/02699050310001645775

17. Boeve B, Wijdicka E, Benarroch E, at al. Paroxysmal sympathetic storms (diencephalic seizures) after diffuse axonal head injury. Mayo Clin Proc. 1998; 732:148-152. https://doi.org/10.1016/S0025-6196(11)63647-1

18. Lemke DM. Riding out the storm: sympathetic storming after traumatic brain injury. J NeurosciNurs. 2003; 36:4-9. https://doi.org/10.1097/01376517-200402000-00002

19. Hinson HE, Sheth KN. Manifestations of the hyperadrenergic state after acute brain injury. CurrOpinCrit Care. 2012; 18:139-45. https://doi.org/10.1097/MCC.0b013e3283513290

20. Heffernan DS, Inaba K, Arbabi S, at al. Sympathetic hyperactivity after traumatic brain injury and the role of beta-blocker therapy. J Trauma. 2010; 69:1602-9. https://doi.org/10.1097/TA.0b013e3181f2d3e8

21. Ley EJ, Park R, Dagliyan G, etal.In vivo effect of propranolol dose and timing on cerebral perfusion aftertraumatic brain injury. J Trauma. 2010; 68:353-6. https://doi.org/10.1097/TA.0b013e3181c8269a

22. Christin L, Ravussin E, Bogardus C, at al. The effect of propranolol on free fatty acid mobilization and resting metabolic rate. Metabolism. 1989; 38:439-44. https://doi.org/10.1016/0026-0495(89)90195-9

23. Welle S, Schwartz RG, Statt M, et al. Reduced metabolic rate during β-adrenergic blockade in humans.Metabolism. 1991; 40:619-22. https://doi.org/10.1016/0026-0495(91)90053-Y

24. Do D, Sheen VL, Bromfield E, et al. Treatment of paroxysmal sympathetic storm with labetalol. J NeurolNeurosurg Psychiatry. 2000; 69:832-3. https://doi.org/10.1136/jnnp.69.6.832

25. Molina PE. Neurobiology of the stress response: contribution of the sympathetic nervous system to theneuroimmune axis in traumatic injury. Shock. 2005; 24:3- https://doi.org/10.1097/01.shk.0000167112.18871.5c

26. Markus T, Hansson SR, Cronberg T, et al. β-Adrenoceptor activation depresses brain inflammation and is neuroprotective in lipopolysaccharide induced sensitization to oxygen-glucose deprivation in organotypic hippocampal slices. J Neuroinflammation. 2010; 20(7):94. https://doi.org/10.1186/1742-2094-7-94

27. Wang J, Li J, Sheng X, et al. Adrenoceptor mediated surgery-induced production of proinflammatory cytokines in rat microglia cells. J Neuroimmunol.2010; 223(1-2):77-83. https://doi.org/10.1016/j.jneuroim.2010.04.006

28. Kato H, Kawaguchi M, Inoue S, et al. The effects of beta-adrenoceptor antagonists on proinflammatory cytokine concentrations after subarachnoid hemorrhage in rats. AnesthAnalg. 2009; 108(1):288-95. https://doi.org/10.1213/ane.0b013e318187bb93

29. Goyagi T, Kimura T, Nishikawa T, et al. Beta-adrenoreceptor antagonists attenuate brain injury after transient focal ischemia in rats. AnesthAnalg. 2006;103: 658-663. https://doi.org/10.1213/01.ane.0000228859.95126.69

30. Mantyh PW, Rogers SD, Allen CJ, et al. Beta 2-adrenergic receptors are expressed by glia in vivo in the normal and injured central nervous system in the rat, rabbit, and human. J Neurosci. 1995; 15: 152-164. https://doi.org/10.1523/JNEUROSCI.15-01-00152.1995

31. Khalili H, Ah R, Paydar S, et al. Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial. World J Surg. 2020; 44:1844-1853. https://doi.org/10.1007/s00268-020-05391-8

32. Ammar MA, Hussein NS. Using propranolol in traumatic brain injury to reduce sympathetic storm phenomenon: A prospective randomized clinical trial.Saudi J Anaesth. 2018; 12(4):514-520. 10.4103/sja.SJA_33_18

33. Nordstrom CH, Messeter K, Sundbarg G, et al. Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg. 1988; 68: 424-431. https://doi.org/10.3171/jns.1988.68.3.0424

34. Asgeirsson B, Grände PO, Nordström CH, et al. Effects of hypotensive treatment with alpha 2-agonist and beta 1-antagonist on cerebral haemodynamics in severely head injured patients. ActaAnaesthesiol Scand. 1995; 39: 347-351. https://doi.org/10.1111/j.1399-6576.1995.tb04075.x

35. Eker C, Asgeirsson B, Grande PO, et al. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med.1998; 26:1881-1886. https://doi.org/10.1097/00003246-199811000-00033

36. Gisvold SE. The Lund concept for treatment of head injuries- faith or science? ActaAnaesthesiol Scand. 2001; 45:399-40. https://doi.org/10.1034/j.1399-6576.2001.045004399.x

37. Wahlstrom MR, Olivecrona M, Koskinen LO, et al. Severe traumatic brain injury in pediatric patients: treatment and outcome using an intracranial pressure targeted therapy-the Lund concept. Intensive Care Med. 2005; 31:832-839. https://doi.org/10.1007/s00134-005-2632-2

38. Tran TY, Dunne IE, German JW, et al. Beta blockers exposure and traumatic brain injury: a literature review. Neurosurg Focus. 2008;25(4): E8. https://doi.org/10.3171/FOC.2008.25.10.E8

39. GhajarJ. Traumatic brain injury. Lancet. 2000; 356 (9233):923-929. https://doi.org/10.1016/S0140-6736(00)02689-1

40. Murry JS, Hoang DM, Barmparas G, et al. Prospectiveevaluation of early propranolol after traumatic brain injury. J Surg Res.2016; 200(1):221-226. https://doi.org/10.1016/j.jss.2015.06.045

41. Cruickshank JM, Degaute JP, Kuurne T, etal.Reductionofstress/catecholamine-induced cardiac necrosis by beta1-selectiveblockade. Lancet. 1987; 2(8559):585-589. https://doi.org/10.1016/S0140-6736(87)92984-9

42. Garg M, Garg K, Singh PK, et al. Neurogenic Fever in Severe Traumatic Brain Injury Treated with Propranolol: A Case Report. Neurol India. 2019; 67(4):1097-1099. https://doi.org/10.4103/0028-3886.266258

43. Meythaler JM, Stinson AM. Fever of central origin in traumatic brain injury controlled with propranolol. Arch Phys Med Rehabil. 1994; 75:816-8. https://doi.org/10.1016/0003-9993(94)90143-0

44. Sazbon L, Groswasser Z. Outcome in 134 patients with prolonged posttraumatic unawareness. Part 1: Parameters determining late recovery of consciousness. J Neurosurg. 1990; 72:75-80. https://doi.org/10.3171/jns.1990.72.1.0075