WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 2, 299-314. Review Article ISSN 2277– 7105

COMA: CURRENT AND EMERGING TREATMENT OPTIONS

R. Sudheer Babu*, K. S. Lakshmi Bhargavi, Sd. Rihana, K. Swathi Sri, K. Durga Prasad and Hankila Ayimchunger

Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur Dt.

Article Received on
23 Nov. 2018,

Revised on 13 Dec. 2018,
Accepted on 02 Jan. 2019

DOI: 10.20959/wjpr20192-14032

***Corresponding Author**
R. Sudheer Babu
Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur Dt.

ABSTRACT

Coma means unarousable, unresponsiveness whereby a patient cannot react with the surrounding environment. It is a state of unconsciousness where by a patient cannot make no localizing responses or discrete defensive movements. Principle causes of coma are diffuse brain dysfunction, drug over dose, alcohol abuse, co-poisoning, hypoxic/ischemic brain injury. Neuronal network in the dorsal Pons and mid brain gives rise to ascending reticular activating system (ARAS) which is responsible for arousal. The CT scan may provide information about the cause of altered mental status and the presence of intracranial hypertension and lumbar puncture (LP) include making an early diagnosis of CNS infection and identification of pathogen, drug sensitivity. Treatment strategies include immediate assessment of airway, breathing, circulation resuscitate, monitoring pulse oximetry. Immediate therapy for hypoglycemia includes giving 50ml glucose IV. Broad spectrum antibiotics, antiviral should be given empirically if there is any suggestion of bacterial infection or encephalitis. Mannitol is indicated acutely for patients who have raised ICP/imminent herniation anti-seizure medications used to treat convulsions in comatose patients. Iron chelation therapy for children with deep coma in cerebral malaria. Methyl phenidate and amantadine used to stimulate reawakening in comatose patients resuscitated from cardiac arrest and in patients with traumatic brain injury. Miraculous recovery from coma by zolpidem. Miraculous herb known as selaginella bryopteris is believed to have unbelievable medicinal value of reviving one from death in coma.

KEYWORDS: Mrita sanjeevani, zolpidem miraculous action in coma, iron chelation therapy, coma in pregnant women, seizures during coma, diabetic coma, myxedema coma.

INTRODUCTION

Coma is a state of profound unresponsiveness, usually the result of a severe brain injury.[3] Comatose patient usually lie with eyes closed and can't be aroused to respond appropriately to vigorous stimuli. A patient in coma can move limbs and have stereotypical withdrawl responses to painful stimuli yet make no localizing responses/discrete defensive movements.[1] If Coma deepens, his response to painful stimuli may diminish.

Stages of Coma

Disorders of consciounesss (DOC) include coma, the vegetative stage (VS) and minimally conscious state (MCS).[2]

COMA: All of the following criteria includes a patient in coma.

- No eye opening, absence of sleep-awake cycles on EEG.
- No evidence of purposeful motor activity.
- No respond to command.
- No evidence of language comprehension/expression.
- Inability to discretely localize noxious stimuli.

Vegetative State

- No evidence of awareness of self/environment.
- No evidence of sustained, reproducible, purposeful, voluntary behavioural responses to visual, auditory tactile or noxious stimuli.
- No evidence of language comprehension/expression.
- Intermittent wakefulness manifested by presence of sleep wake cycles.
- Sufficiently preserved hypothalamic and brain stem automatic functions to permit survival with medical and nursing care.
- Bowel and bladder incontinence.
- Variably preserved cranial nerve reflux and spinal reflexes.

Minimally Conscious State

- Simple command following.
- Gesture or verbal yes/no responses.
- Intelligence verbalization.
- Movement or effective behaviours that occur in contingent relation to relevant environmental stimuli and aren't attributable to reflexive activity.

- Pursuit eye movement/sustained fixation that occurs in direct response to moving/salient stimuli.
- Episodes of crying, smiling or laugh in response to language/visual content of emotional but not neutral topics/stimuli.
- Vocalizations/gestures that occur in direct response to the linguistic content of comments/questions.
- Reaching for objects that demonstrates a clear relation between object location, direction of reach.
- Touching/holding objects in manner that accommodates the size and shape of the object.

Persistent Vegetative State

It is a DOC in which patients with severe brain damage are in state of partial arousal rather than real awareness. After 4 weeks in a vegetative state the patient is classified as in a persistent vegetative state. This is often regarded as permanent vegetative state some months after a non-traumatic brain injury/1 year after a traumatic injury. Nowadays the scientist call this as apallic syndrome.[4]

Aetiology

In coma brain stem is often injured. The brain stem process automatic unconscious control called the vegetative functions of human that includes HR, BP, temperature, breathing.[5] The reticular activating system is located within the brain stem and is important "on/off" switch for consciousness and sleep. If persons looses consciousness it may be either due to RAS stopped working/both central hemispheres have shutdown.

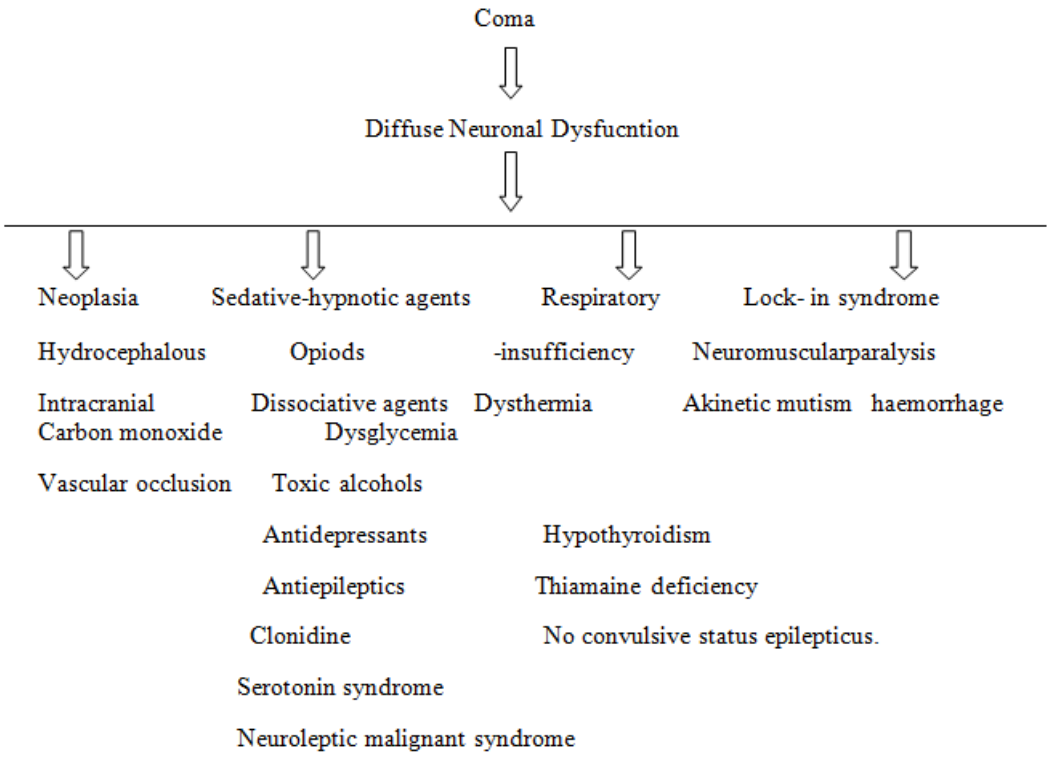
RAS stop working either due to:

1) Brainstem bleeding/loss of oxygen, this shuts off RAS.

2) Swelling in the brain due to which intracranial pressure in brain increases causing compression of the brain tissue against the skull bones which in turn changes the breathing and blood pressure control of brain which leads to brain death.

Causes of Coma

Casual overview of coma and coma mimics



Causes of persistent vegetative state: It may be caused due to

1) Acute traumatic brain injury.[6]
2) Non traumatic: Neurodegenerative disorder/metabolic disorder of the brain
3) Severe congenital abnormality of the CNS.
4) Vascular pressure causing intracranial haemorrhage.
5) Hypoxic ischemic injury.
6) Trauma, seizures.
7) Electrolyte imbalance.
8) Sepsis.

Coma Mimics

- The locked-in syndrome (paralysis of all voluntary muscles of body) usually as a result of ischemia/infarction to CNS tracts like PONS.[7]
- Neuromuscular paralysis may be iatrogenic, after administration of succinylcholine/curare like drugs, blue ringed octopus, toxin of clostridium botulinum, venom of elapid snakes.[8]
- Akinetic mutism usually results from injury to frontal/pre frontal motor cortex.[9]

- Psychogenic unresponsiveness a complex disorder in which there is no neurologic insult, the condition resolves spontaneously.[10]

Pathophysiology

Coma was attributed to the damage of neuronal pathways that ascend from brainstem in the setting of diffuse axonal injury to the hemispheric white matter. A neuronal network in the dorsal Pons and midbrain gives rise to (ARAS) ascending reticular activating system which is responsible for arousal. Neurons from these centers run together through the thalamus and then to the bilateral cerebral cortex; the cortex controls sensory processing and understanding, which generates awareness.[11] Coma results from an impairment of this axis by a process that affects the brain arousal center, consciousness center, the tracts that connect them, or some combination thereof. Although the final common pathway of coma is neuronal dysfunction in the ARAS thalamic –cortical pathway it is useful to subdivide the pathophysiology into structural versus diffuse neuronal dysfunction. Structural causes of coma are defined as those that precipitate cellular dysfunction through a mechanical force. Diffuse neuronal dysfunction precipitates coma by abnormalities only at cellular level and may be further divided into 2 general categories 1) Toxic 2) Metabolic. In a toxin induced coma, an exogenous substance is responsible for the clinical findings. In a metabolic coma, a perturbation of an endogenous process such as temperature/sodium regulation, has gone invalid. A metabolic process such as hypoglycemia/hypoxia may initially produce coma through diffuse neuronal dysfunction. However, if the process is uncorrected and cell death occurs, the cause of coma becomes structural.

Clinical Signs

- Most important clinical signs identifying those patients with a poor outcome are the brain stem reflexes, and the simple tests of corneal reflexes and papillary responses, as identified by Jorgensen.[12]
- There are some clinical signs which predict a good outcome of the development of nystagmus on occulo vestibular testing or the vocalization of any recognizable word within 48hrs indicates a 50% likelihood of good recovery and the presence of motor localizing within 1st 24hrs indicates a 20% chances of recovery.

Clinical Manifestations

Vital signs

1. Pulse: Bradycardia may occur in the context of sympatholytic drugs such as clonidine. In setting of sedative hypnotic toxicity, particularly with the use of barbiturates and gamma hydro butyrate. Tachycardia is common with psychotropic drugs poisoning, ketamine intoxication these produce coma via symptomatic hyponatremia.[13]

2. Blood pressure: Hypotension may occur in sepsis and many poisonings particularly tricyclic. Antidepressants, clonidine, sedative hypnotic agents.

3. Respiratory rate: Tachypnea is common with metabolic acidosis of any cause. Bradycardia may be seen in both opiod and sedative hypnotic toxicity.

4. Examination of head may show obvious signs of deformity such as crepitus or bony steps-off or in setting of a skull-fracture.

5. Eyes: Miosis is commonly seen in opiod and clonidine toxicity. mydriasis is seen in poisoning with compounds having anticholinergic properties (Tricyclic antidepressant) and MDMA.

6. Ears: Hemotympanum seen in 50% of basilar skull fractures.[14]

7. Skin: Excessively dry skin due to poisoning with a drug with anticholinergic properties such as tricyclic antidepressants, coma bullae associated with barbiturate toxicity.[15]

Diagnosis

- Electrophysiological tests include somato sensory evoked potential (SSEP)-Measures electric signals of sensation that travels from body to brain.
- Electroencephalogram (EEG).

Biochemical tests

- These tests include proteins such as serum neuron specific enolase (NSE)S-100 and creatinine kinase, brain isoenzyme (CKBB). Other tests may measure brain oxygenation and intracranial pressure.
- Serum NSE level ≥ 33mcg/lit measured to 1-3 days after CPR accurately predict poor recover.

Brain imaging studies

- CT Scan, MRI, PET Scan- Taking pictures of brain structure function.
- Lumbar puncture: Performed if meningitis/encephalitis is suspected.
- Severity of coma can be assessed by Glasgow coma scale.

Glasgow coma scale = E+M+V (Eye opening +Motor response+verbal response)

GCS minimum =3

GCS maximum=15

- Generally coma classified as: Severe- GCS ≤8

  Moderate- 9 to12

  Minor- GCS ≥13

Glasgow coma scale and full outline of unresponsiveness (Four) score

Glasgow coma scale	Full outline of unresponsiveness score
Eye opening response Spontaneously, 4 To speech, 3 To pain, 1 Best verbal response Oriented, 5 Disoriented, 5 Inappropriate words,4 Incomprehensible sounds, 3 No response, 1 Best motor response Obeys command,6 Localize pain, 5 Withdrawl from pain, 4 Decorticate flextion, 3 Decerebrate extension, 2 No movement, 1	Eye response Open and tracking or blinking to command, 4 Open but not tracking, 3 Closed but open to loud voice, 2 Closed but open to pain, 1 Close with pain, 0 Motor response Thumbs up, fist or peace sign, 4 Localize pain, 3 Flexion response to pain, 2 Extension response to pain, 1 No response to pain or myoclonic status, 0 Brain stem reflexes Pupil and corneal reflexes present, 4 1 pupil wide and fixed, 3 Pupil or corneal reflexes absent, 2 Pupil and corneal reflexes absent, 1 Absent pupil, corneal and cough reflex, 0 Respiration Not intubated, regular pattern, 4 Not intubated, cheyne-stokes pattern, 3 Not intubated, irregular breathing, 2 Breathes above ventilator rate, 1 Breathes at ventilator rate or apnea, 0

Duration of Coma

Coma can last from several days to several weeks. In more severe case last over five weeks, while some as long a several years. After this time patients gradually come out of coma, some progress to a vegetative state and others die.

Coma in Pregnant Women

If a woman is pregnant and undergoes coma. Treating coma in the mother also means treating the fetus. Pregnancy is possible and generally not a health risk while most paralyzed women can have normal vaginal deliveries, certain complications of pregnancies like hormonal

effects on blood volume, blood vessels and changes in blood pressure explain some cause of stroke in pregnancy, intracranial hemorrhage, venous occlusive disease. Worsening of underlying vessel disease during pregnancy delivery and postpartum period.

Coma in Infants

Comatose state of an infant may be much more difficult to recognize and is often confused with physiological sleep states. An infant is considered to be in coma when there is no appropriate response to shaking, pinching, visual/auditory stimuli. Considering the size of infant and child, number of relatively severe falls, trauma excluding the battered baby is a relatively infrequent cause of coma.[16]

Recovery from Coma

Coma: Structural brain damage to both cerebral hemispheres with or without injuries to tegmental midbrain, rostral pons or both isolated bilateral injuries to midline tegmental midbrain, rostral pons/both.

- Functionally intact brain stem, normal arterial blood gases.

Vegetative: Spontaneous cycling of eye opening and closing grimacing and non purposeful movements usually able to ventilate without mechanical support.

Emergence, phase 1

- Cessation of anaesthetic drug.
- Reversal of peripheral muscle relaxation.
- Transition from apnea to to regular breathing.

Emergence, phase 2

- Increased heart rate and B.P.
- Return of autonomic responses.
- Responsiveness to painful stimulation.
- Salivation (7^{th} and 9^{th} cranial nerve muclei).
- Grimacing.
- Swallowing, gagging, coughing.
- Return of muscle tone.
- Defensive posturing.
- Further increase in α and β activity on EEG.
- Extubation if possible.

Emergence, phase 3

- Eye opening.
- Responses to oral commands.
- Awake patients on EEG.
- Extubation possible.

Minimally conscious state

- Purposeful guarding movements.
- Eye tracking.
- Inconsistent communication, verbalization.
- Following oral command.
- Return of sleep –wake cycles.
- Recovery of normal sleep-wake cycle.

Coma Alarm

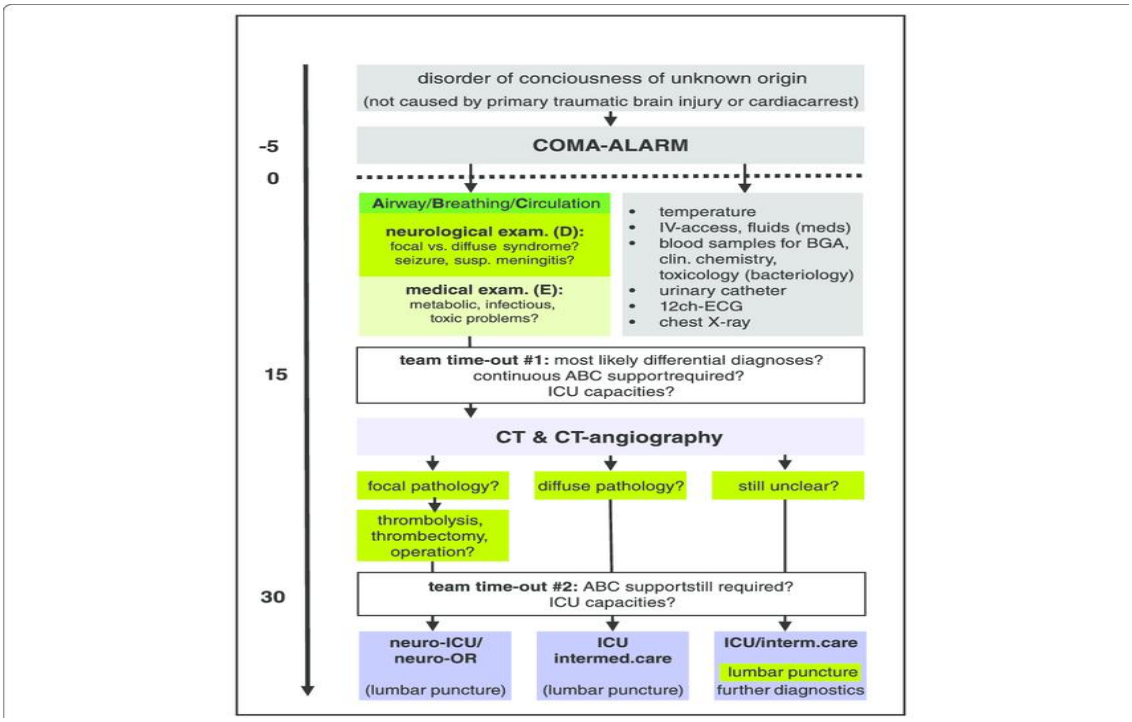
A new management protocol termed as coma alarm for emergency patients presenting to hospital with a disorder of consciousness with all obvious origin such as cardiac arrest/TBI.

In order to identify whether patient is eligible for new protocol the following is considered :

A) If patient is reported to be fully awake when contacted by paramedics/emergency physicians.

B) If there is evidence of primary TB.

If both are invalid then a non-traumatic disorder of consciousness of unknown origin is considered and staff are instructed to trigger newly implemented coma alarm.



Abnormal Movements in Comatose Patients

Coma is a state of unresponsivenesss due to various type of brain injuries[18] different types of abnormal movements may be seen which represent motor paroxysms in the setting of cerebral herniationn, such as flexor/extensor posturing secondary to severe brain injury and subsequent cerebral edema.

Table:[19]

Abnormal movements	Definition
1. Chorea	Involuntary, purposeless, nonrhythmic, non-sustained movements that flow from one body part to the other Hemiballismus; a severe form of cholera, is characterized by vigourus irregular high amplitude movements on one side of the body.
2. Clonus	Rhythmic involuntary muscular contractions and relaxations
3. Dystonia	Sustained twisting movements that are often frequent and progresses to prolonged abnormal postures.
4. Myoclonus	Sudden, brief involuntary movements which may be caused by muscle contractions (positive myclonus).
5. Shivering	High frequency involuntary muscular contractions involving one group or more of muscles.
6. Tremor	Oscillatory rhythmic movements that affects one or more parts of the body.

Iron chelation therapy for deep coma patients in children with cerebral malaria

It involves the administration of chelating agents to remove heavy metals from body, several chelating agents like desferoxamine, deferasirose used to prevent iron overload and is

administered intravenously (100/kg body wt) along with placebo, standard therapy with quinine and sulfadoxine pyremethamine. Desferal enhances the clearance of p.falciparum parasitemia in patients with asymptomatic infection.[20] Iron serve as a redox agent in generation of free radicals that mediate ischemic and hemorrhagic tissue injury.[21,22] Desferal inhibits peroxidase which damage CNS.[23]

Myxedema Coma

It is a state of decompensated hypothyroidism. A stressful event like myocardial infarction, stroke precipitates myxedema coma. It is a loss of brain function as a result of long standing low level of thyroid hormone in the blood. In myxedema coma conversion of T4-T3 is impaired.[24] It is usually treated with T3 initially and start T4 as well.

Diabetic Coma

It is a reversible form of coma found in people with diabetes mellitus. It is a medical emergency.[25] Different types of diabetic coma are identified as

- Severe low blood sugar.
- Diabetic ketoacidosis (usually type-1 D.M) advanced enough to result in unconsciousness from a combination of severely increase in blood sugar levels, dehydration, shock and exhaustation.
- Hyperosmolar nonketotic coma (usually type-2 D.M) in which extremely high blood sugar level and dehydration alone are sufficient to cause unconsciousness.
- ✓ Treatment includes IV fluids, insulin and administration of K+ and Na+ for ketoacidotic diabetic coma.
- ✓ Plenty of IV fluids, insulin, K+ and Na+gives as soon as possible for hyperosmolar diabetic coma.

Seizures During Coma

- A single seizure rarely produce coma but continuous seizures called status epilepticus can prevent the brain from recovering in between the seizures. This will cause prolonged unconsciousness /coma.
- Seizures can happen in 1-5 of every 10 people who have had a TB, depending on whether the injury occurred in the brain.
- During a seizure there will be a sudden abnormal electric disturbances in the brain that results in one/more of the following:

1. Unresponsiveness and staring.

2. Chewing, lipsmatching/fumbling movement.
3. Strange movement of head, body, legs/eyes such as stiffening/shaking.

- Antiepileptic drugs like carbamazepine, phenytoin are used to control seizures.

ICU Management of Hypertension in Comatose Patient

Main goal of care include optimizing cerebral blood flow (CBF)/Cerebral perfusion pressure (CCP) and minimizing factors that increase ICP (Intra Cranial Pressure).

1. Assess the airway, breathing and circulation (ABCS).
2. Assess and treat for immediately correctable cause of coma.
3. Assessment of the depth of coma.
4. Assessment and treatment of raised ICP.

Mannitol- Used in patients in whom there is strong suspicion of raised ICP/imminent herniation.[26] Mannitol has 2 distinct effects.[27,28,29] The immediate effect is decrease blood viscosity resulting in a transient increase CBF followed by a more sustained fall in CBF. The delayed osmotic effects occur after 15-30 min and last for 4-6 hrs.

Hypertonic saline (HTS)- It acts like mannitol by maintaining a constant osmolar gradient in order to draw fluid from brain parenchyma without the risk of dehydration and tubular damage in hypotensive/hypoperfused patients.

Fluid therapy: Hypovolemia worsens outcome in children with meningitis, malaria[30] and severe head injury.[31] Hypovolemic lowers the CPP and lead to worse ICP due to auto allergy vasodilation.[32]

Hypotonic fluids like 5% dextrose can exacerbate cerebral edema and ICP.[33-34]

Methyl phenidate and amantadine to stimulate reawakening in comatose patients resuscitated from cardiac arrest, traumatic brain injury: Treatment with phenidaate may provide neurostimulations by augmenting the activity of injured neuronal tissue within the reticular activating system and by amplifying the net effect of the reduced no. of viable neurons. Patients receiving neurostimulants trended towards improved rate of following commands, survival to hospital discharge and distribution of CPC and mRS scores.

Zolpidem miraculous action in comatose patient: Louis viljoen, a 24 years old boy went into deep coma. After 5 years of coma Dr. Wally Nel prescribed a sedative stilnox

(zolpidem). After taking the drug he rotated his head and shown auditory responses. Louis has given stilnox everyday for 7 years. Although the effects of the drug are supposed to wear off after about 2 and a quarter hours and zolpidem power as sedative means it cannot simply be taken evrytime a patient slips out of consciousness, improvement continues as if long-dormant pathways in his brain are coming back to life. Zolpidem use in patients shown about 60% improvement and is remarkable. After scanning Louis they detected that areas that appeared black and dead before had began to light up with activity afterwards, improvements in left parietal lobe and the left lentiform nucleus were visible which are important for motor function, sight, speech, bearing.

Nel and Clauss have a hypothesis that after brain has suffered severe trauma a chemical known as GABA closes down brain function in order to conserve energy and help cells survive. However in longterm dormant state, receptors in brain cells that respond to GABA become hypersensitive and as GABA is a depressant it causes persistent vegetative state. It is believed that during this process the receptors in some way changed/deformed so that they respond to zolpidem differently from normal receptors. Thus breaking the hold of GABA. This could mean instead of sending patients to sleep it makes dormant areas of the brain function again and some comatose patients wake up.

Indian magical herb selaginella bryopteris (Mrita sanjeevani) for comatose patients: It is a lithophylic plant located in between Balangir and Bargarh distinct of odisha. It is believed to have the unbelievable medicinal effect of reviving one from death. Sanjeevani means (one that inculcates life). The herb has a startling nature of coming back to life if submerged in water for 15 min even from year old dry stage.

Chemical constituents: 384 mg/g protein.

118.075 mg/g insoluble carbohydrate.

8.4 mg/g soluble carbohydrate.

1.423 mg/g chlorophyll

0.6 mg/g phenol.

Secondary metabolites: Alkaloids, flavanoids, steroids, saponins, cardiac glycoside and tannins showed positive result.

An acute oral toxicity study of selaginella bryopteris at dose from 250-2000 mg/kg body weight. It is useful to the coma patient by the way of inhalation.[35] This is hypothesized that this herb has growth promoting activity as well as protective action against stress-induced cell death and play vital role in organism growth, development, tissue homeostasis and maintenance of genomic integrity.

CONCLUSION

There are very few studies and known treatment strategies for coma. More studies with promising systemic therapies and combination treatments are needed. In this review we focus on the newer treatment strategies for comatose patients which include Iron chelation therapy for deep coma in cerebral malariae, Zolpidem miraculous action, Herbal treatment with bryopteris selaginella which plays a great role in growth promotion, protection against stress induced cell death.

ACKNOWLEDGEMENT

I am very thankful to professor Sd.Rihana, S.k Karishma for generously supplying the impressive record and for her assistance in our clinical work. I would like to thank all my co-authors who assisted me in doing this work.

Conflicts of Interest Statement

None of the authors have conflicts of interest with respect to this work.

REFERENCES

1. Review article on general anesthesia, sleep and coma by Emery N.Brain, M.D., ph.D, Ralph Lydic ph.D and Nicholas, D.schiff M.D.
2. Berube J, Fins, Giarciro J, et al, The mohank report. A report to congress. Disorders of consciousness: Assessment, treatment and research needs, 2011.
3. Posner J, saperc, Schiff N, Plum F, Plum and Posners diagnosis of stupor and coma. Newyork: oxiford universirt press, 2007.
4. Laureys, Stoven, Celesia, Gastone G, Cohadon, Francosis, Lauri J Sen, Jan, Leon-carrion, Jose, Sannita, Walter G, Sazbon, Leon, Schmultzhard, erich, Von wild, Klaus R, "unresponsiveness wakefulness syndrome: a new mame for vegetative state/apallic syndrome". BMC mediane.
5. Understanding stages of coma-Rainbow rehabilitation centers http://www.rainbow.rehab.com.

6. Lippincott, Williams and Wikins (2001). In a page: Paediatric signs and symptoms.
7. Cardwell MS. Locked-in syndrome. Tex med., 2013; 109: 21.
8. Bawaskar HS, Bawaskar PH. envenoming by the common Krait (Bungarus Caeruleus) and Asian coba 9Naja Naja): clinical manifestations and their management in rural setting. wilderness environ med, 2004.
9. Ackermann H, Ziegler W.Akinetic mutism- a review of the literature (review) Fortschr Neural psychiatry, 1995; 63(2): 59-67.
10. Baxtor CL white WO.psychogenic coma: Case report Int J psychiatry Med, 2003; 33(3): 317-22.
11. Sarasso S, Rosanova M, Casali AG, et al. Quantifying cortical EEG responses to TMS in unconsciousness clin EEG Neuro sci., 2014; 45(1): 40-9.
12. Jorgensen EO, Malchow-Moller, A Natural history of global and critical brain ischaemia. Rosusatation, 1981; 9: 133-91.
13. Traub SJ, Hoffmann RS, Neison's. The "ecstasy" hangover: hyponatremia due to 314-methylene dioxy methamphetamine. J urban health, 2002.
14. LIU-Shindo M, Hawkins DB. Basilar skull fractures in children. Int J pediatry otorhinolaryngol, 1989; 176.
15. Bosco L, Schena D, Colatoc C. Coma blisters in children. Case report and review of the literature. J child neural, 2013; 28(IL): 1677-80.
16. Caffey J: The whiplash Shaken infant. Pediatrics, 396-403, 1974.
17. Review article on general anesthesia, sleep, coma by emery N.Brown, M.D.ph.D Ralph lydic, ph.D, and Nicholas D, Schiff, M.D.
18. Stevens RD, Bhardwaj: A approach to comatose patient. Crit care med., 2006; 34: 31-41.
19. Towne AR, Waterhoyse EJ, Baggs JG, Garnett LK, Brawn AJ, Smith Jr JR, etal. Prevalence of nonconvulsive status epilepticous in comatose patienys neurology, 2000; 54: 340-5.
20. Gordeuk VR, Thuma PE, Brittenham GM, et al. Iron chelation wuth desferioxamine B in adults with asymptomatic plasmodium falciparum parasite blood, 1992; 19: 308-11.
21. Sadrzadeh SMH, Graf e, Panter Ss, Halloway PE, Eaton JW. Hemoglobin: a biologic fenton reagent. J Biol chem., 1984; 259: 14354-6.
22. Ward PA, Till GO, Hatherill JR, Annesley TM, kunkel RG. Systemic complement activation, lung injury, and products of lipid peroxidation. J Clin Invest, 1985; 76: 517-22.

23. Sadrzadeh SMH, Anderson DK, Panter SS, Hallaway PE, Eaton JW. Hemoglobin potentiates central nervous system damage. Jolin Inveet, 1987; 79: 662-4.
24. Chatzitomaris, Apostolos, Hoermann, Rudolf, Midgley, John E, Herning, Steffen, urban, Aline, Diet rich, Barbara, Abood, Assjana, Klein, Harald M, dietrich, Johannes W(20 july 2017). "Thyroid allostasis- Adaptive responses of thyrotropic feedback control tp conditions of strain, stress, and development orogramming".
25. Richard S.Irwin, James M. rippe (2008). Irwin and Rippes intesnsive care mediane Lippincotte Williams and Wilkins PP 1256-ISBN 978-0-7817-9153-3.
26. Lorsen GY, Vernon DD, Dean JM. Evaluation of the comatose child in: Rogers MC, ed. Textbook of pediatric intensive care, 3rd edition, Battimore; Williams and Wilkins, 1996; 735-745.
27. Lorsen GV, Vernon DD, Dean JM. Evaluation of the comatose child in: rogers MC, ed. Textbook pediatric intensive care, 3rd edition, Battimore; Williams and Wilkins, 1996; 735-745.
28. Mayer SA, chong JJ. Critical care management of increased intracranial pressure. J Intensive care Med., 2002; 17: 55-58.
29. Packlznsk, RP. Osmotherapy: basic concepts and controversies, crit care clin., 1997; 13: 163-185.
30. Maittand k, Levin m, severe P.falciparum malaria in Kenyan children. Evidence for hypovolamia. OJ med., 2003; 96: 427-434.
31. Mazzola CA, Adelson PD. Critical care management of head trauma in children. crit care Med., 2002; 30: 3393-5401.
32. Mayer SA, Chong JJ. Critical care management of increased intracranial pressure. J Intensive care Med, 2002; 17: 55-58.
33. Kirkhan FJ. Non-traumatic coma in children Arch Diz child, 2001; 85: 303-312.
34. Rosner MJ, Rosner SD, Johnson AH. Cerrebral perfusion presuure, management protocol and clinical results. J Neurosurgeon, 1995; 83: 949-962.
35. Sah, Nk; Singh, SN; Sahdaw, S, Banerji, S; Tha, v; kahn; z; Hasnain, SE. "Indian herb" sanjeevahi (selaginella btryopteris) can promote growth and protect against heat shock and apoptotie activities of ultraviolet and oxidative stress". Journal of bio sciences, September 2005; 30(4): 499-505.