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Review Article | Palliative Medicine & Care: Open Access | Open Access

The Role of Palliative Care in Adult Moderate to Severe Traumatic Brain Injury

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Received: May 28, 2018; Accepted: July 16, 2018; Published: July 24, 2018

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Abstract

Moderate to severe traumatic brain injury is one of the most common causes of death and major disability among adult patients. The change of quality of life that patients experience should trigger physicians to practice palliative care principles and when needed, to consult specialty palliative care. The role of palliative care in the management of moderate to severe traumatic brain injury in adults has not been well studied. Furthermore, there are palliative care issues specific to patients with traumatic brain injury that need to be studied. This review describes available literature on the role of palliative care in the management of patients with moderate to severe traumatic brain injury. It also highlights the need for further studies in palliative care and the management of devastating traumatic brain injuries and its impact in overall healthcare system and the patients' and caregivers' quality of life.

Keywords: Role of Palliative Care; Brain Injury; Trauma; Causes of death

Introduction

Traumatic brain injury (TBI), "a silent epidemic" is a public health issue that contributes to major disability in both national and global setting [1, 2]. Because of the potential for significant chronic disability and higher likelihood of death among those with moderate to severe brain injuries, discussions on the goals of care of a patient should ensue the soonest possible time. Studies on the impact of palliative care specifically in adult traumatic brain injury are sparse however in the advent of specialized neurocritical care and Neurotrauma units as well as a growing body of palliative care specialists, it is important to review the role of palliative care in the setting of adult moderate to severe traumatic brain injury [3]. In this review we will discuss the epidemiology, severity and impact on outcomes of traumatic brain injury in the adult population and then discuss palliative care as a part of the holistic management of traumatic brain injury.

Traumatic Brain Injury

Traumatic brain Injury (TBI) is "an alteration in brain function, or other evidence of brain pathology, caused by an external force" [4]. It represents one of the major public health problems affecting more than 1.7 million persons annually in the United States and causing 31% of all injury-related deaths [5]. Patients with TBI suffer a wide variety of symptoms and lifelong disabilities with approximately 43% of hospitalized TBI patients developing long-term disabilities [6, 7]. Despite the recent decrease in mortality rates; the disability rates from TBI have not changed [8].

A higher incidence of TBI in children aged 0–4 years, adolescents aged 15–19 years, and adults aged 75 years and older compared to other age groups were noted in the Centers for Disease Control report, and the highest rates of deaths from TBI was from adults aged more than 75 years old [5]. Falls (35%), motor vehicle-related injuries (17%), and blows to the head (17%) were reported as the most common causes of non-fatal TBI [9]; while, most of TBI-related deaths were linked to motor vehicle crashed (31.4%) and firearm-related events (34.8%) [10].

The damage from TBI can be immediate (primary) that usually develops from the initial traumatic impact causing; focal brain bleeding, contusion, and bruising or diffuse axonal injury that result from acceleration and deceleration. Secondary injuries occur as an indirect effect of the initial insult which later can lead to brain ischemia and edema, hypoxia, raised intracranial pressure, hypotension, and seizures [6, 11, 12].The severity of TBI is classified into mild, moderate, and severe based on their clinical presentation using the Glasgow Coma score (GCS) where GCS 14-15 is mild and 3-8 is considered severe [11, 13].

Complications from TBI include but are not limited to behavioral dysfunction, seizures, spasticity and multi organ dysfunction, all of which affect their quality of life and functionality. Many patients with severe TBIs will have good outcomes and will be capable of functioning independently, however some may end up with severe disabilities or in a persistent vegetative state, that will require long term care, and will have significant impact on families and care givers producing substantial emotional, behavioral and relationship difficulties [12, 14-17].Moreover, TBI has major economic implications owing to the hospital care and rehabilitation costs, (direct cost), in addition to the loss of

productivity of those patients (indirect cost). Several studies have examined the annual cost of TBI in different countries. In the United stated, the total cost estimate of TBI management ranges from $60 billion up to $76.5 billion [18, 19]. Gustavsson and his colleagues developed a cost model for different brain disorders in about 30 European countries. They found that the direct medical cost of TBI was €5085 million per year [20]. In 2007, a study in Spain found that the economic costs for TBI patient range between USD 1.5 - 5.5 billion annually [21]. In UK, the aggregate cost of TBI was estimated to be £15 billion without including the indirect cost [22]. In Australia, the total indirect and direct costs were estimated to be $8.6 billion with $4.8 billion attributed to severe TBI [23]. A study was done in Ontario, showed that the approximate direct cost of TBI in Canada was $331.1 million in the first follow up year [24].

Because of the severity of illness in TBI patients and its subsequent burden on families, their care during the inpatient and outpatient phases requires an interdisciplinary team approach consistent of rehabilitation and palliative care (PC) services to assist in dealing with the challenges they face during their recovery period [12,25].

Palliative Care Role among Patients with Moderate to Severe Traumatic Brain Injury

The World Health Organization has most recently defined palliative care (PC) as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [26].There has been increasing recognition of the role of PC among patients with neurological conditions which became more evident in the establishment of the American Academy of Neurology Ethics and Humanities Subcommittee. [27]. In the critical care setting where death is common, there is more awareness of the importance of palliative care involvement [28] however studies in the setting of traumatic brain injury are lacking. Table 1 summarizes literature available specifically studying palliative care and traumatic brain injury. One retrospective study of TBI patients in a palliative care center revealed that those with moderate to severe TBI receive tracheostomies and gastrostomies at a rate of 61% and 67% respectively with issues regarding lack of mobility, nutritional complications and pressure ulcer formation [3]. The authors

Table 1: Summary of Studies regarding Palliative Care and Traumatic Brain Injury

Study	Objective and Study design	Study population and methodology	Results	Remarks
Traumatic brain injury and palliative care: a retrospective analysis of 49 patients receiving palliative care during 2013-2016 in Turkey. [3]	Retrospective study to investigate PC requirement, hospitalization period and discharge status of TBI patients in the PC center in Turkey.	Patients admitted in the PC center of Ankara Ulus State Hospital, Turkey diagnosed with TBI with complete records during the period of 2013-2016 were included. Patients grouped according to GCS, GOS and KPS severity, presence or absence of mobilization, PEG, tracheostomy, oral nutrition and pressure ulcer and discharge disposition and compared.	-49 patients included in the study -Overall characteristics: 71% males, mean age 45.4±20.2 years, median GCS 10 (IQR4). -Most common cause to trauma is MVA -most patients had severe GCS, GOS of severe disability, and severe KPS. -Most patients had no mobilization, oral nutrition or pressure ulcer while majority had a tracheostomy and gastrostomy	-Also described trends of variables according to GCS, GOS and KPS
Palliative Care Consultations in the Neuro-ICU: A Qualitative Study. [29]	Qualitative study to identify content and themes of PC consultation, analyze the reason for it and describe the most common recommendations of PC specialists.	Patients admitted from January 1, 2014 who were admitted to the Harborview Medical Center neuro-ICU whose admission was at least 24 hours and who had a PC consultation were included through retrospective EHR review. Coding scheme was prepared by investigators which included 15 primary codes and 17 subcodes and the coding and content analysis was performed by a web-based qualitative data analysis software program. The number of cases analyzed was determined by the matic saturation, when there were no available new themes from their gathered data.	-Included 25 neuro-ICU patients (4.1% of all neuro-ICU admissions from January to August 2014.) -stroke and TBI comprised of 1/3 of patients -most common reason for consultation is "clarifying goals of care" -4 clinical issues stressed in palliative care consultations include discussions about prognosis, patient and family values, understanding medical options and identifying conflicts. -the most common category of PC consultant recommendations involved ways to be on the same level of communication with the individual patient and/ or family	-Unique study design -Provides idea on how to approach palliative care themes for patients with TBI in the neuro-ICU -described contrast of palliative care needs of patients with acute brain injury versus those with cancer, as well as patients in the neuro-ICU versus the medical ICU.

Withdrawal of care: a 10-year perspective at a Level I trauma center. [30]	Retrospective review of Withdrawal or limitation of care in trauma patients to identify the population of patients undergoing WLC and to describe the process of trauma surgeon -managed WLC.	Trauma patients admitted from 2000 through 2009 at Scripps Mercy Hospital were reviewed and WLC was determined from the review of the Trauma Medical Director's dictated death summaries.	-Among 698 deaths, 375 (53.7%) occurred with WLS -10-year rate of WLC 50%-61.1% -WLC increased by 1% per year increase in age -1% of the patients were under palliative medicine at the time of death -WLC was associated with increased age, lower injury severity, falling mechanism, Charlson index and Trauma consult. -Most common mode of WLS was withdrawal of care (74.1%) -goals of care were discussed within 24 hours of admission. -most common conflict was differences between physicians and family among those with conflicts -palliative care was ordered in 5.9% of non-organ harvest TS-managed WLC	-first detailed description of the prevalence, clinical presentation and TS-managed process of WLC at an adult Level I trauma center -WLC was defined as "withholding CPR protocols, withdrawing medications, laboratory and other testing, mechanical ventilation, and all other measures that would otherwise be indicated and not related to the comfort of the patients" -3 modes of WLC based on patient status at death: care withdrawn, limited or no resuscitation, organ harvest for organ donors. - describes guidelines that enumerates elements of TS's WLC.
Surrogate decision making for patients with severe traumatic brain injury. [31]	Prospective qualitative study to describe how surrogates made the decision to withdraw or continue life support and whether they believed that health care team could have assisted more during the decision-making process.	Prospective recruitment of surrogates through the patients' trauma surgeons or neurosurgeons. Semi structured interviews were conducted with surrogates. Questions included what decisions did the surrogate make, how those decisions were made, if in their view the health care team could have been more helpful, is there anything they would change about the process and if they will make the same decisions after time has passed.	-10 surrogates agreed to participate up to 11-20 months after the patients' severe TBI occurred -decisions made by surrogates mostly revolved around withdrawing or continuing life support and surgical procedures, 50% of them withdrew life support. -decisions were influenced by prior conversation, prognosis, quality of life, burden of treatment, prayer, "gut" instinct and statistics. -some deferred to the physicians and described those decisions as "making no decisions" -themes that arose from the interviews included: reliance on resources to inform decision making, frustration with the physicians' limited availability and communication skills and role of another health care professional and appreciation for ICU nurses' help.	-gives a great insight on SDM -limitation is the sample size

PC=palliative care, TBI= traumatic brain injury, GCS= Glasgow Coma Scale, GOS= Glasgow Outcome Scale, KPS= Karnofsky Performance Scale, PEG= Percutaneous Endoscopic Gastrostomy, ICU= Intensive Care Unit, EHR= Electronic Health Record, WLC= Withdrawal or limitation of care, TS= Trauma Surgeon, CPR= Cardio-pulmonary Rescuscitation, SDM= Surrogate decision maker.

surmised that due to the multitude and complexity of the health status of TBI patients it is important to involve PC earlier on starting in the ICU also to improve the quality of life of these patients. (Table 1)

Moderate to severe TBI (msTBI) are one of the most common acute neurological conditions seen in the neurocritical care unit (NCCU) due to its high risk of death with mortality ranging from 12% - 61.2% [32, 33]. It was also found to be one of the most common diagnosis that entailed specialist PC consultation [34]. The needs of palliative care specifically in the NCCU were mostly for social support and establishing goals of care [34]which are both important in patients with TBI in the ICU especially the geriatric assault patients with TBI who have been found to be sicker with higher mortality and poorer outcomes compared to younger patients [33]. The Improving Palliative Care in the ICU project recommendation to select triggers for PC consultation among critically ill patients include an ICU admission with a hospital stay greater than or equal to 10 days, age more than 80 years old with two or more life-threatening co morbidities (as defined by the Acute Physiology and Chronic Health Evaluation II definitions of severe chronic organ insufficiency), a diagnosis of active stage IV malignancy, status post cardiac arrest; or a diagnosis of intracerebral hemorrhage requiring mechanical ventilation [35-37].

In line with stroke recommendations, neurologists are expected to provide primary PC while in tackling more complex issues, it is recommended to involve specialist PC earlier on [38]. In primary PC, the primary team handles discussions regarding goals of care and prognostication as they manage patients' symptoms management [39] this level of PC has also been termed as Basic PC [40] Specialty palliative care is an interdisciplinary team that consists of the PC physician, nurse practitioner, nurse, social workers and spiritual providers [38] who are trained and who continue to update their skills and knowledge [40] with regards to providing palliative care.

Timing of PC in Moderate to Severe TBI

Palliative care should be initiated when the patient is in the ICU for msTBI especially since the condition is serious, life-threatening and potentially may cause a decrease quality of life (QOL). This recommendation is similar to what is recommended for stroke patients and this should be applied to msTBI patients as well [38]. Two models PC involvement in the ICU has been recommended by the Improving Palliative Care in the ICU (IPAL-ICU) Project after they reviewed existing data [36, 41-45]. The "consultative model" increase the involvement of PC consultants in the care of the patients and their families in the ICU especially those at risk of poor outcomes while the "integrative model" encourages the utilization of PC principles by the primary ICU team for all ICU patients [41]. Awareness of these models should enable appropriate PC level of care of the ICU patients as can be applied to msTBI patients. In addition, reasons to initiate PC consultation has been reported which can be based on baseline patient characteristics (pre-morbid condition, age more than 80 years old), selected acute diagnoses (global cerebral ischemia, prolonged multiple organ dysfunction), and/or health care based criteria such as specified duration of ICU treatment, tracheotomy or gastronomy referral [41, 46-47]. Such triggers can encourage PC involvement sooner. More studies are needed to determine the impact of trigger-based or model-based specialty PC involvement in msTBI patients.

Challenges in the Neuro ICU and Patients with Moderate to Severe TBI

Decision Making Capacity

Impaired medical decision-making capacity (MDC) is prevalent in acute TBI and is strongly related to injury severity. Capacity compromise being evaluated as understanding, reasoning, and appreciation occurred in 10%-30% of patients with mTBI, 50% of patients with cmTBI, and 50%-80% of patients with msTBI [48]. However in the ICU, in the acute setting when msTBI patients are in a comatose state surrogate decision makers (SDM) assume the main decision making capacity. Unconscious patients are considered vulnerable in terms of their ability to consent for medical procedures or ongoing therapy [49]. Also note that a patient with msTBI may have fluctuating level of consciousness wherein memory can be recovered, consciousness may be recovered intermittently to a level that may allow a patient to make decisions, or a patient may stay comatose indefinitely. Unfortunately, laws delineating limits of when a patient with msTBI who is conscious or minimally conscious is able to consent is lacking except for the comatose or vegetative state [49, 50]. The doctrine of informed consent allowed a legal representative or an SDM to make decisions for the patient based on their knowledge of the patient's beliefs and wishes [49] which is still not an ideal way to make decisions [51]. Although most states allow advance directives such as living will and healthcare power of attorney legal documents, most of the acute msTBI patients are young, who are likely not to have these documents in place. Although 44 states allow that healthcare surrogates can make decisions without going through court, the requirements for surrogacy may vary among states and even institutions [49, 52]. Hierarchy and Consensus surrogate consent laws exist today except for the seven states with no surrogate consent laws (Massachusetts, Minnesota, Missouri, Nebraska, New Hampshire, Rhode Island and Vermont). Hierarchy consent laws delineate the order by which the patient's family can be considered as SDM. Majority of the states follows this order: the spouse (unless divorced or legally separated); adult child; parent then an adult sibling. Some states further describe the order to include almost all living relative [52]. In states where SDM are decided by consensus, the "interested persons" agree on who will be the SDM. In this case, "interested" persons include a spouse, reciprocal beneficiary, any adult child, and either parent of the

patient, an adult sibling or adult grandchild or any adult who showed exceptional concern for the patient who is aware of the patient's values [52-54]. Decision making is not well delineated in cases where patients do not have living relatives or friends, who can be involved in decision-making, namely the "unbefriended" patients [55-57]. Once the SDM has been selected, in the cases of availability of family or friends, the surrogates must decide on patient issues based on substituted judgement standard. In this case, the SDM refers to the patient's inferred wishes based on the patient's values and statements [52, 58]. The best interest standard delineates that the SDM will use the patient's welfare when making decisions if the patient's wishes are generally unknown [52, 58].

In Europe, the SDM hierarchy differs between countries. For example, in Belgium, Spain, Switzerland, and Netherlands, if the patient has no SDM, a close relative such as spouse, parents, children or siblings represent the patient. In UK, there are two types of surrogates; a designated power of attorney by the patient and an official representative appointed by the court. However, only the power of attorney can make decisions regarding withdrawal of care, and in case of their absence, it becomes the physician responsibility to make this decision. In Germany, there are similar types of surrogates as in UK, but with equal power, and if there is a disagreement regarding the life sustaining measures, the court's approval is required [59]. Canada and Australia have similar laws as most countries, where the appointed SDM tops the list followed by relatives in the following order: spouse, child, parent, sibling [60, 61]. In Japan, there is no clear law for SDM. Consents to treat are generally obtained from family members based on the traditional Japanese family structure [61].

Prognostication in TBI

Given principles to adhere to in decision making for a patient with msTBI as discussed in the prior section, one of the biggest challenges is how to factor in the prognosis of the patient. Surrogate decision makers consider injury severity, potential functional neurologic outcome and likelihood of worsening neurologically or progression to death [62]. One of main difficulty facing palliative care in Neuro ICU and TBI patients is that prognosis differs widely between different physicians in different institutions as shown in a recent survey [63] as well as the presence of various prognosticating models specifically in the area of TBI [64, 65] that has recently been updated to be able to incorporate laboratory and radiologic findings. Table 2 gives a summary of common prognostic scores and models used in TBI. Further complicating prognostication is the varied clinical experiences of physicians that affect the accuracy of their prognostication [62, 64]. Known independent predictors of unfavorable outcome in TBI patients at 6 months is increased age [74] while age >65, low GCS score, high intracranial pressure, abnormal pupillary reactivity and abnormal laboratory values such as low hemoglobin, low platelets and high glucose have shown association with worst outcome [75]. Early withdrawal of life support (WLST) defined to be withdrawal of care prior to 72 hours [76] in the setting of a severe brain injury has been thought to be affected by the physician's self-fulfilling prophecy in which the patients have poor outcome when they have a predicted low likelihood of favorable outcome and not treated aggressively [75]. It is concerning that in a cohort of sTBI patients, 20% of the deaths were associated with WLST decision [77]. In another cohort, it was found that the 10-year rate of withdrawal or limitation of care was 50-61.1% which increases by 1% per year increase in age [30]. And of note, all of those for which WLST was undertaken died. Herniation on the initial CT scan was found to increase the likelihood of WLST while the finding of an epidural hematoma on CT scan and surgical interventions such as craniotomies or laparotomies decrease the odds of death after WLST [77] and this may give us an idea regarding decision making surrounding WLST. It has been strongly recommended that WLST should not be done prior to 72 hours [78]. In a study done in Canada, they showed that among severe TBI patients WLST occurred before 72 hours in 50% of the patients [79] this area represents an area of opportunity in terms of further research into varied practices of intensivists when faced with decisions of WLST especially in cases of msTBI. (Table 2)

Table 2: Common prognostic scores and models in Traumatic Brain Injury

Score	Component	Remarks
Glasgow Coma Scale Score [66]	-assess patient's responsiveness in terms of Eye, Verbal and Motor responses -range 3-15	-widely used as an index of brain injury which can be used in estimating prognosis
Glasgow Coma Scale- Pupil (GCS-P) [67]	-GCS-P= GCS-PRS, where PRS is the pupil reactivity score -PRS =1, if 1 pupil unreactive to light -PRS =2, if 2 pupils unreactive to light -PRS=0, if both were reactive to light -range: 1-15	-outcome 6 months after injury -quick to calculate
SIRS (Systemic Inflammatory Response Syndrome) score [68]	-SIRS score calculated by assigning 1 point for each SIRS criterion present on admission which include: Body temperature <36°C or >38°C, Heart rate >90 beats per minute, Respiratory rate >20 breaths ber minute and white blood cell count <4000 mm3 or >12,000 mm3. -Range 0-4	-predictive of length of stay and mortality in trauma patients -for isolated TBI, SIRS present on admission is a predictor of poor outcome -each SIRS criterion was found to be independent predictor of negative outcome -Body temperature was the strongest predictor

International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) in TBI prognostic model () [69]	-calculate predictions with complex models -predicts mortality and 6-month unfavorable outcome -calculator available http://www.tbi-impact.org/?p=impact/calc for the Core IMPACT score, it includes Age, GCS Motor Score and Pupil reactivity -for the Core + CT model, includes Hypoxia, Hypotension, Marshall CT Classification, presence of traumatic subarachnoid hemorrhage and epidural mass on CT -for the Core + CT + Lab model, glucose and hemoglobin were considered	-based on analysis of multiple clinical trials in traumatic brain injury -population limited to those enrolled at the time of the clinical trials included -includes brain imaging and laboratory values -8509 patients from 8 RCTs and 3 observational studies
Abbreviated Injury Scale for Head or Neck Regions [70]	-For the head and neck, Injuries rated 1-6 from minor to major injuries -include Brain stem: laceration, crush, penetrating or transecting injury -and C3 or higher complete cord transection or contusion	-anatomy-based coding system to classify and describe severity of injuries -used for single injuries
Marshall-CT classification (M-CT) [71]	-classifies patients into 6 CT findings based on intracranial pathology, cisterns presence, midline shift, volume of lesions and lesion evacuation -Diffuse injury I-IV, Evacuated mass lesion, non-evacuated mass lesion	-based on 746 patients with severe TBI -has been shown to predict outcome on its own and has been included in various prediction models
Rotterdam-CT classification (R-CT) [72]	-includes degree of basal cistern compression, midline shift, presence of epidural hematomas, intraventricular blood and/or subarachnoid blood. -Range: 1-6	-predicts mortality at 6 months (Maas AI, Hukkelhoven CW, Marshall LF et-al. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2006;57 (6): 1173-82)
Corticosteroid Randomisation After Significant Head Injury trial data (CRASH) model [73]	-Basic model and CT model -prediction of outcome in all TBI severity groups -predicts unfavourable outcome at six months and mortality at 14 days -Basic model: Age, GCS motor score, pupil reactivity and major extracranial injury -CT model: Basic Model variables + CT classification and traumatic subarachnoid hemorrhage -calculator found in: http://www.crash.lshtm.ac.uk/Risk%20calculator/	-similar to IMPACT model, was developed utilizing large datasets -based on the CRASH trial dataset (n=10008) with patients who have mild-severe TBI in low and middle-income countries. -used IMPACT data set for external validation
PRS=pupil reactivity score, SIRS= systemic inflammatory response syndrome, TBI= traumatic brain injury, IMPACT= International Mission for Prognosis and Analysis of Clinical Trials, CT= Computed tomography, RCT= randomized clinical trials, AIS= Abbreviated Injury Scale, M-CT= Marshall CT classification, R-CT= Rotterdam-CT classification.		

Tracheostomy and Gastrostomy

Patients with msTBI usually undergo endo tracheal intubation with subsequent feeding tube placement in the acute setting of their care since their level of alertness and other neurologic functions cannot protect the airway nor coordinate and effective swallowing mechanism to support the patients' nutritional requirements. The dilemma is how to predict among the msTBI who will require long term Tracheostomy with or without gastrostomy placement. In a cohort of 375 patients with sTBI, it was found that Tracheostomy tube placement, increased age, low Rancho Los Amigos score and aphonia on the initial swallowing evaluation increased the possibility of requiring a feeding tube when discharged [80]. Younger age and private insurance on the other hand were found to be independent predictors of

Tracheostomy placement among sTBI patients [81]. Palliative care involvement in this setting should not be limited to those withholding these procedures. Palliative care has a role before and after these procedures especially because msTBI patients who receive both a Tracheostomy and a gastrostomy most likely will have a significant change in their quality of life. In a study looking at patient characteristics in a palliative care center, it was found that 65% of the patients had a Tracheostomy while 71% had a gastrostomy [3]. This same cohort also had more than 50% proportion of patients having severe disability and vegetative state combined [3]. Also note that in the stroke population, dysphagia has been found to be a predictor of transition to palliative care [82] in relation to the subsequent discussion of goals of care and artificial nutrition. This is applicable to patients with msTBI where in Tracheostomy and gastrostomy placements are frequent.

Paroxysmal Sympathetic Hyperactivity

Paroxysmal Sympathetic Hyperactivity (PSH) is a complication of severe acute brain injuries most commonly msTBI and has been described in the setting of ischemic or hemorrhagic stroke, encephalitis and anoxic injury [83]. It has been also known as "storming", Dysautonomia, autonomic storming [83], diencephalic seizures [84] and other terms to reflect its typical symptomatology which usually includes tachycardia, hypertension, tachypnea and diaphoresis [84]. Its etiology is unknown however it has been proposed that disconnection from inhibitory centers damaged by the brain injury leaves an intact sympathetic drive to be hyperactive [83]. Its occurrence has been found to influence outcome in terms of longer ICU stay and higher incidence of infections [85]. Furthermore, it has been found not only to occur in the acute hospitalization but even up to 1-year post-injury [76]. It has been reported in a patient in permanent vegetative state for which palliative care played a role in controlling the symptoms by early recognition and appropriate treatment [86]. The limitation that may be encountered in its management in the palliative care setting may include the route of administration of medications usually given to manage PSH. There are no treatment guidelines on the management of PSH however several publications have recommended medications to target specific symptoms [83, 84, 87]. Table 3 shows management options for PSH [88, 89] in the palliative care setting considering limited access for the patients with the goal of providing comfort. Increased awareness and case finding are needed to further research on the management of PSH in the palliative care setting. (Table 3)

Table 3: Management options for Paroxysmal Sympathetic Hyperactivity in the palliative care setting [88, 89]

Medication	Possible Mechanism of action	Targeted symptoms	Dosage	Available route
Morphine	Opiate agonist	Pain	Starting dose: intravenous: 1 – 2 mg every 1 – 2 hours as needed Maximum dose: N/A (titrated to patient response)	Intravenous, oral
Benzodiazepine	GABA-A agonist	Anxiety, rigidity, spasticity	Dependent on specific benzodiazepine	Intravenous (lorazepam, diazepam, midazolam), oral (lorazepam, diazepam, midazolam, clonazepam), rectal (diazepam)
Baclofen	GABA-B agonist	Spasticity	Starting dose: 5 mg every 8 hours Maximum dose: 80 mg/day	Oral
Clonidine	α2-adrenergic agonist	Hypertension, tachycardia	Starting dose: 0.1 mg every 8 hours Maximum dose: 2.4 mg/day	Oral, patch
Propranolol	Nonselective β-adrenergic antagonist	Tachycardia, hypertension	Starting dose: 10 mg every 8 - 12 hours Maximum dose: 640 mg/day	Oral
Bromocriptine	Dopamine D2 agonist	Hyperthermia, sweating, hypertension	Starting dose: 2.5 – 5 mg every 8 hours Maximum dose: 40 mg/day	Oral
Gabapentin	Voltage-gated calcium channel antagonist	Pain, spasticity	Starting dose: 300 mg every 8 hours Maximum dose: 3600 mg/day	Oral

The Effect of Palliative Care on Outcome

Several studies evaluated the effect of specialized palliative care on outcomes in patients with advanced illness. A systematic review published in 2017 showed that the early integration of palliative care in those patients can improve their quality of life (physical, psychological or social), especially in cancer patients. However, there was no significant effect on symptoms burden, psychosocial aspects, survival time, place of death, and cost of care [90].

The data regarding the effect of palliative care on critically ill patient caregivers is mixed. Some studies showed some benefits to caregivers' quality of life and satisfaction [91]. Khandewal et al. [91] conducted a systematic review on the effect of palliative care on ICU utilization; they found that patients who received a palliative care intervention had a reduced ICU length of stay, and a decreased rate of ICU admissions [92]. Moreover, it was reported that the quality of end of life care improved with early implementation of don't resuscitate (DNR) orders, as a result of prolonging the time spent by the patients with their families and loved ones while receiving active palliative care [93]. Over the past few years, there has been a significant increase in the health care expenditure in USA. The introduction of specialized palliative care services in hospitals thought to reduce health care costs by avoiding unnecessary investigations and prolonged ICU/hospital stay [94]. In 2011, a study examined the effect of palliative care consultations on hospital costs for Medicaid beneficiaries in patients with life threatening conditions. They found that hospital costs were less by $6,900 in patients who received a PC consult compared to those received the usual care, with estimated savings of $84 million to $252 million annually in Medicaid's spending [95].

Recent Studies have empathized the growing needs for palliative care services among patients with neurologic diseases [34, 96]. Interventions provided through palliative care services can play a crucial role in enhancing TBI patients' and care givers' quality of life, decision-making, and emotional distress. Furthermore, the expected increase in TBIs rates over the next few years with the concomitant growth of their cost of care requires implementing different strategies to help in reducing the economic burden associated with this condition. It is possible that the early integration of palliative care in the care of these patients could aid in lowering their health care costs and improving outcomes; stemmed from previously published reports on the effect of palliative care on outcomes of critically ill patients [93-95]. Having said that, there is limited data regarding the effect of palliative care on traumatic brain injury patients, and further research is needed to delineate the importance of PC interventions in this specific cohort.

Conclusion

Palliative care plays an important role in the management of patients with moderate or severe TBI from the beginning of the hospitalization until the post-discharge and rehabilitation phase. Further research need to be done to explore and study research gaps such as epidemiology of PC in msTBI patients, impact of care in this specific population and management approaches towards msTBI patients in the setting of palliative care.

Conflicts of Interest

None

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