ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

HETEROTOPIC OSSIFICATION

POST ACQUIRED BRAN INJURY

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Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI) *Heterotopic Ossification post Acquired Brain Injury.* Through the collaboration of researchers and clinicians and supported by the Ontario Neurotrauma Foundation/Ontario Ministry of Health, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and has been committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto), Dr. Shawn Marshall (University of Ottawa) and Dr. Nora Cullen (McMaster University) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Heather MacKenzie, MD, FRCPC is a consultant physiatrist in the spinal cord injury and brain injury rehabilitation programs at Parkwood Institute in London, Ontario, and an assistant professor in the Department of Physical Medicine & Rehabilitation at Western University. Her research focuses on the development of prognostic models and predicting outcomes after mild traumatic brain injury and concussion. Most recently, she completed a Master of Science degree in Epidemiology at the Harvard T. H. Chan School of Public Health.

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Dr. Shawn Marshall is a physician specializing in Physical Medicine and Rehabilitation (Physiatrist). He is the Division Head of Physical Medicine and Rehabilitation at the University of Ottawa and The Ottawa Hospital where he manages both in-patients and out-patient clinics for patients with concussion to severe traumatic brain injury. Dr. Marshall has a Master's degree in Clinical Epidemiology and is a Full Professor at the University of Ottawa in the Department of Medicine.

Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies (Table 1).

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amytrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA).

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours

Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–April 2022 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury, and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality RCTs (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate, and the intensity in which it should be provided, based on their assessment of the patient. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with these limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	PCT	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post test	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

HETEROTOPIC OSSIFICATION

POST ACQUIRED BRAIN INJURY

Summary of the Evidence

Intervention	Key Point Level of Evidence
PROPHYLAXIS OF HETEROTOPIC OSSIFICATION	
Pharmacological Interventions	
Nonsteroidal Anti-inflammatory Drugs	Further research is necessary to determine the efficacy of nonsteroidal anti-inflammatory drugs for the prevention of heterotopic ossification in individuals with ABI.
Etidronate Disodium	Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI. - *There is level 2 evidence (Spielman et al., 1983) that etidronate disodium may reduce the incidence of heterotopic ossification in individuals with severe ABI when compared to no intervention.*
MANAGEMENT OF HETEROTOPIC OSSIFICATION	
Non-Pharmacological Interventions	
Forceful Joint Manipulation	Forceful joint manipulation may be effective in preventing bony ankylosis, as well as in increasing range of motion in joints affected by heterotopic ossification post TBI. - *There is level 4 evidence (Garland et al., 1982) that forceful joint manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification post TBI.*
Extracorporeal Shock Wave Therapy	Extracorporeal shock wave therapy may be effective for the management of pain and/or range of motion associated with heterotopic ossification in TBI populations. - *There is level 4 evidence (Reznik et al., 2017; 2017) that extracorporeal shock wave therapy may reduce pain associated with heterotopic ossification and improve range of motion in individuals with TBI.*
Radiation Therapy	Radiotherapy may be effective for the management of pain and range of motion associated with heterotopic ossification in individuals with ABI. - *There is level 4 evidence (Lee et al., 2016) that radiation therapy may decrease pain, improve range of motion and prevent further formation of heterotopic ossification in ABI populations.*
Surgical Interventions	
Surgical Excision	Surgical excision of may improve range of motion and functional outcomes in ABI populations with heterotopic ossification. Early surgical excision may not increase the risk of recurrent heterotopic ossification. - *There is level 3 evidence (Genet et al., 2012) that early surgical excision may not increase the recurrence risk of heterotopic ossification compared to delayed surgical excision.*

- *There is level 4 evidence (Fuller et al., 2013; Genet et al., 2009; Fuller et al., 2005; de Palma et al., 2002; Ippolito et al., 1999a; Ippolito et al., 1999b; Ippolito et al., 1999c; Charnley et al., 1996; Kolessar et al., 1996; Moore et al., 1993; Melamed et al., 2002; Lazarus et al., 1999) that surgical excision may improve range of motion and functional outcomes in ABI populations with heterotopic ossification.*

Introduction

Heterotopic Ossification (HO) is the formation of pathologic bone within soft tissues, often muscle tissues, where bone formation does not usually occur (Watanabe & Sant, 2001). HO may be conceptualized as a form of aberrant tissue repair that can result from musculoskeletal trauma (e.g., fractures), an injury to the nervous system, or surgical procedures such as hip, knee, shoulder or elbow arthroplasty (Shehab et al., 2002). The incidence of HO in patients with traumatic brain injury (TBI) has been reported to range from 11% to 77% but is clinically relevant in 10-20% (Dizdar et al., 2013; Garland et al., 1980; Rogers, 1988; Sarafis et al., 1999; Simonsen et al., 2007; Zychowicz, 2013). Risk factors include skeletal trauma, spasticity, diffuse axonal injury, mechanical ventilation, prolonged immobilization, and injury severity (Huang et al., 2018; Moreta & de los Mozos, 2014). HO is often quite painful and limits joint mobility; the restricted joint range of motion may exacerbate disability and impede progress towards desired rehabilitation goals.

Formation of Heterotopic Ossification

The pathophysiology of HO is not fully understood. Mesenchymal stem cells are multipotent adult stem cells capable of generating cartilage, bone, muscle, tendons, ligaments, or fat (Pape et al., 2004); It is thought that they play a pivotal role in the development of HO (Williams et al., 1999). The development of HO begins with the formation of osteoid, periarticularly and intramuscularly, and progresses to full calcification within a matter of weeks; over the next few months, the calcified osteoid remodels into well-organized trabecular bone at which point it is considered to have matured (Pape et al., 2001). Several months after the inciting event, patients with HO begin to experience restricted range of motion, pain, and potentially ankylosis (Banovac & Gonzalez, 1997; Garland et al., 1980). The bony lesion has been found to have a high metabolic rate, with a rate of bone formation more than three times greater than that of normal bone, and an osteoclastic density of more than twice the density found in normal bone (Puzas et al., 1987).

There are neurogenic factors contributing to HO, although the mechanisms are not entirely clear yet (Brady et al., 2018; Hurvitz et al., 1992; Moreta & de los Mozos, 2014; Pape et al., 2001; Pape et al., 2004) It has also been noted that circulating factors promoting HO may be present in patients with head injuries (Pape et al., 2004). Many studies have shown enhanced osteogenesis in patients sustaining TBI (Trentz et al., 2005). The presence of certain hormonal factors early post injury influences the stimulation of osteoprogenitors within skeletal muscles; further, tissue hypoxia, sympathetic changes, immobilization,

remobilization, and spasticity are additional risk factors (Ivanhoe et al., 2012). Accelerated fracture healing and HO are well documented phenomena in these patients (Bidner et al., 1990; Keret et al., 1990).

Clinical Presentation

Among individuals with TBI, the most common sites of HO are the soft tissues around the hip, elbow, shoulder, and knee (Almangour et al., 2016; Garland, 1991; Garland et al., 1980; van Kampen et al., 2011; Vanden Bossche & Vanderstraeten, 2005). The hip is the most frequent site of ossification (Dizdar et al., 2013; Vanden Bossche & Vanderstraeten, 2005), with total ankylosis of the joint occurring in 5-16% of affected hips (Stover et al., 1991). HO of the shoulder has been found to affect 5% of individuals with a brain injury (Cipriano et al., 2009), while the knee is a less common site for HO following brain injury (Sarafis et al., 1999). When HO is present in the knee, it is usually seen medially (Hosalkar et al., 2013). The distribution of HO around the elbow occurs most commonly either anteriorly in the flexor muscles or posteriorly in the extensors (Sarafis et al., 1999). Of the joints affected by HO after brain injury, ankylosis is most likely to occur in the posterior elbow (Garland et al., 1980).

The formation of HO in individuals with brain injuries tends to occur within one to three months after the brain injury (Brady et al., 2018; Vanden Bossche & Vanderstraeten, 2005; Zychowicz, 2013). Pape et al. (2004) noted that clinical examination in the setting of HO may reveal a swollen, warm, painful joint which is often associated with decreased range of motion. The earliest sign is typically a loss of range of motion in the involved joint (Watanabe & Sant, 2001). Other indicators include erythema, palpation of a periarticular mass, and fever (Varghese, 1992). Because of the association with fever, it is sometimes difficult to differentiate HO from infection (Citta-Pietrolungo et al., 1992; Garland, 1991; Garland et al., 1980). Moreover, the clinical picture may be confused with deep vein thrombosis (DVT), local trauma, or fracture (Buschbacher, 1992; Jensen et al., 1987). HO will then progress from these initial symptoms into a mass with stiffness and induration; in addition, potential complications of HO include compression of blood vessels and nerves, breakdown of associated tissue, restricted motion, and loss of function (Zychowicz, 2013).

Diagnostic Testing

HO may be difficult to diagnose in the early stages due to the non-specificity of the associated signs and symptoms (Shehab et al., 2002). Furthermore, plain radiographs will usually remain normal until ossification begins at approximately 4-6 weeks post onset. Serum levels of alkaline phosphatase, a glycoprotein in the plasma membrane of osteoblasts, and the erythrocyte sedimentation rate may become elevated early on but are non-specific. The triple phase technicium-99 bone scan remains the diagnostic gold standard. The test is positive if there is increased uptake during the first and second

phases of the study. This test typically becomes positive when clinical features appear (i.e., before an x-ray would be positive).

In the HO literature there are several classification systems, such as the Brooker classification or the Hastings and Graham classification (Ranganathan et al., 2015). The Brooker Classification system is the most widely used system to classify ectopic-bone formation after total hip replacement. The system is based on anteroposterior radiographs of the pelvis and the categorization of the progression of HO into classes (Brooker et al., 1973). Brooker et al. (1973) defined Class I as islands of bone within soft tissues about the hip; Class II as bone spurs from the pelvis or proximal end of the femur with at least 1cm between opposing bone surfaces; Class III as bone spurs from pelvis or proximal end of the femur, reducing space between opposing bone surfaces to less than 1cm; and Class IV as apparent bony ankylosis of hip. This classification system has been criticized for high inter-observer variability and poorly addressing information relevant to cases of neurogenic HO (Della Valle et al., 2002; Mavrogenis et al., 2012; Toom et al., 2005).

PROPHYLAXIS OF HETEROTOPIC OSSIFICATION

The development of HO in patients with TBI is difficult to predict, making preventative treatment challenging. Prophylactic treatment options for HO include range of motion exercises, nonsteroidal anti-inflammatory medications, low-dose radiation, and etidronate disodium (EHDP) (Watanabe & Sant, 2001). Research on the efficacy of these treatments in patients with TBI is limited, and generally focused on secondary prevention after treatment of established HO. Further investigation is needed to develop more effective preventative treatments (Brady et al., 2018).

Pharmacological Interventions

Nonsteroidal Anti-Inflammatory Drugs

The evidence for nonsteroidal anti-inflammatory medications as prophylactic treatment for HO stems mostly from the use of indomethacin or ibuprofen in patients following total hip arthroplasty (Fransen & Neal, 2004; Kjaersgaard-Andersen & Schmidt, 1986; Ritter & Sieber, 1985). In patients with spinal cord injuries, preliminary studies of indomethacin or selective Rofecoxib (a selective COX-2 inhibitor) have shown decreased incidence of HO (Banovac et al., 2004; Banovac et al., 2001). Although it has been reported that the prophylactic use of these medications significantly decreases HO formation following total hip arthroplasty, it is not known if these medications have the same effect in the ABI population.

KEY POINTS

- Further research is necessary to determine the efficacy of nonsteroidal anti-inflammatory drugs for the prevention of heterotopic ossification in individuals with ABI.

Etidronate Disodium

Etidronate disodium (EHDP) is a bisphosphate drug that has been used for prophylaxis and treatment of HO in individuals with burn injuries (Orchard et al., 2015). However, there is limited evidence on the use of EHDP for prophylaxis of HO in other populations, including individuals with ABI.

TABLE 4 | Etidronate Disodium (EHDP) for Prophylaxis of Heterotopic Ossification post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Spielman et al. (1983) USA PCT N=20	**Population:** Head Injury; Gender: Male=16; Female=4. *Intervention Group (n=10):* Mean Age=31yr; Mean GCS=5.2. *Control Group (n=10)*: Mean Age=27yr; Mean GCS=5.5. **Intervention:** The intervention group received Etidronate Disodium (EHDP) (20 mg/kg/day for 12wk, 10 mg/kg/d for next 12wk) within 2-7d post injury which continued for 6mo. The control group did not receive EHDP. **Outcome Measures:** Presence of fractures, development of HO.	1. The EHDP treated group showed a significantly lower incidence of HO compared with controls (2 versus 7 patients, p<0.025). 2. Of the 9 that developed HO, 25 sites were affected; elbows (35%), shoulders (29%), hips (18%), and knees (18%) were most common. Seven individuals had restricted limb motion and 2 had ankylosis.

Discussion

In PCT study, Spielman et al. (1983) found that patients treated with EHDP showed a significantly lower incidence of HO than controls. However, due to the small sample size of the study, additional research assessing the benefit of EHDP for the prevention of HO following brain injury is needed.

Conclusions

There is level 2 evidence (Spielman et al., 1983) that etidronate disodium may reduce the incidence of heterotopic ossification in individuals with severe ABI when compared to no intervention.

KEY POINTS

- Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI.

MANAGEMENT OF HETEROTOPIC OSSIFICATION

As HO can be challenging to initially diagnose and has high recurrence rates (Almangour et al., 2016), it is important to determine which interventions are successful for the direct treatment of HO. Unlike patients with spinal cord injury, the cognitive and functional status of patients with ABI is not a predictor of recurrence; therefore, it is more difficult to determine which patients are most likely to re-develop HO, reinforcing the need for effective interventions (Almangour et al., 2016).

Non-Pharmacological Interventions

Forceful Joint Manipulation

Recent studies have shown that there are potential alternatives for the treatment of HO other than surgery, which is invasive and can be inefficient in terms of recurrence rates (Lee et al., 2016). At one time, the literature on range of motion therapy post ABI suggested that such experiences contributed to the development of HO (Chantraine & Minaire, 1981; Crawford et al., 1986). A shift in practice then occurred towards the utilization of range of motion exercises, and even joint manipulation under anesthesia, to help prevent ankylosis in patients with ABI (Garland, 1991; Garland et al., 1982). Although not specific to patients with ABI, careful and judicious use of physiotherapy involving assisted range of motion exercises and gentle stretching may be beneficial for HO; however, caution is required when moving the joint, as mobilization beyond its pain-free range of motion can exacerbate the condition (Evans, 1991; Pape et al., 2004).

TABLE 5 | Forceful Joint Manipulation for the Management of Heterotopic Ossification post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Garland et al. (1982) USA Case Series N=16	**Population:** TBI; Mean Age=24yr; Gender: Male=8, Female=8; Mean Time Post Injury=3.6mo. **Intervention:** Records of patients who received forceful manipulation under general anesthesia were reviewed. The 28 manipulated joints included: 11 hips, 13 elbows, and 4 shoulders. Mean follow-up time was 15mo. **Outcome Measure:** Degree of motion.	1. Gains in range of motion were made in 23 joints (82%). 2. Eighteen joints (64%) maintained or gained further motion with rehabilitation after manipulation. 3. Seven hips (63%) gained an average of 52°, 8 elbows (62%) gained an average of 47°, 3 shoulders (75%) increased in degree of external rotation.

Discussion

In a case series, Garland et al. (1982) reviewed patients with TBI and pre-existing HO who underwent forceful manipulation of joints under anesthesia and reported that 82% of joints gained range of motion. The authors concluded that forceful manipulation under anesthesia is useful in maintaining motion, aids

in the prevention of bony ankylosis, and does not appear to exacerbate the ossification process (Garland et al., 1982).

Conclusions

There is level 4 evidence (Garland et al., 1982) that forceful manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification post TBI.

KEY POINTS

- Forceful joint manipulation may be effective in preventing bony ankylosis and increasing range of motion in joints affected by heterotopic ossification post TBI.

Extracorporeal Shock Wave Therapy

The aim of shock wave therapy is to disrupt unwanted bone formations through vibration (Reznik, Biros, Lamont, et al., 2017; Reznik, Biros, Sacher, et al., 2017). Shock wave therapy has been used to mitigate pain, strengthen the muscle, and increase range of motion of both joints and extremities in a variety of musculoskeletal conditions (Li et al., 2022).

TABLE 6 | Extracorporeal Shock Wave Therapy for the Management of Heterotopic Ossification post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Resnik et al. (2017) Australia Pre-Post $N_{initial}$=11, N_{final}=9	**Population:** TBI=11; Mean Age=41yr; Gender: Male=9, Female=2. **Intervention:** Patients with TBI and chronic neurogenic heterotopic ossification (NHO) at the hip or knee received 4 applications of high-energy extracorporeal shock wave therapy (ESWT) delivered to the affected joint over 8wk (one treatment every 2wk). **Outcome Measures:** Faces Rating Scale (FRS) for pain; NHO size.	1. Patients receiving high-energy ESWT experienced a significant reduction in pain intensity from baseline to post-intervention as measured by the FRS (p=0.002). 2. There was no significant mean difference from baseline to post-intervention in NHO size.
Resnik et al. (2017) Australia Pre-Post $N_{initial}$=11, N_{final}=11	**Population:** TBI=11; Mean Age=41yr; Gender: Male=9, Female=2. **Intervention:** Patients with TBI and chronic neurogenic heterotopic ossification (NHO) at the hip or knee received 4 applications of high-energy extracorporeal shock wave therapy (ESWT) delivered to the affected joint over 8 wk. **Outcome Measures:** Range of motion (ROM); Functional Reach (FR); Modified Functional Reach	1. Patients receiving high-energy ESWT showed significant improvement in ROM (flexion) of the NHO-affected knee (p=0.002, n=4) from baseline to post-treatment. No significant effects of treatment on knee extension w observed. No significant results were found for hip ROM. 2. Patients receiving high-energy ESWT showed significant improvement in FR

Author Year Country Study Design Sample Size	Methods	Outcome
	(MFR).	(p=0.006, n=5) score from baseline to post-treatment. No significant effect of treatment on MFR scores was observed.

Discussion

Two pre-post studies by Resnik et al. (2017; 2017) examined the use of extracorporeal shock wave therapy (ESWT) in a population with TBI and HO. The authors found that ESWT was successful in reducing pain associated with HO and that patients experienced a significant improvement in the flexion range of motion of affected knees; however, no significant effects were seen on knee extension or hip range of motion (Reznik, Biros, Lamont, et al., 2017; Reznik, Biros, Sacher, et al., 2017).

Conclusions

There is level 4 evidence (Reznik et al., 2017; 2017) that extracorporeal shock wave therapy may reduce pain associated with heterotopic ossification and improve range of motion in individuals with TBI.

KEY POINTS

- Extracorporeal shock wave therapy may be effective for the management of pain and/or range of motion associated with heterotopic ossification in TBI populations.

Radiation Therapy

The aim of radiotherapy is to disrupt mesenchymal stem cell differentiation into osteoblasts during the early phases of HO (Balboni et al., 2006); by doing so, additional bone formation at a specific site should be arrested. Radiation therapy has been used in oncology populations with progressive HO located in hip, femur and knees (Lee et al., 2020).

TABLE 7 | Radiation Therapy for the Management of Heterotopic Ossification post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Lee et al. (2016) Korea Pre-Post	**Population:** TBI=1, Meningioma=1, Spontaneous Intracranial hemorrhage=1; Mean Age=37yr; Gender: Male=3; Mean Time Post Injury=4.5yr. **Intervention:** Three cases of neurogenic HO were	1. All 3 patients had decreased serum ALP, decreased BALP levels, decreased pain, and increased joint ROM immediately after RT.

Author Year Country Study Design Sample Size	Methods	Outcome
$N_{initial}$=3, N_{final}=3	treated with radiation therapy (RT). Patients received 10 days of RT for a total dose of 20 Gray (Gy) in 2 Gy fractions to each affected joint. The results of 4-6mo follow-up evaluation after brain injury are reported. **Outcome Measures:** Serum alkaline phosphatase (ALP) level; serum bone-specific ALP (BALP); HO involved joint range of motion (ROM); pain severity.	2. No further growth of the HO was seen on post-treatment imaging. 3. At 4 or 6 months after RT, all patients maintained clinical and laboratory improvements.

Discussion

In a pre-post study, Lee et al. (2016) examined the effects of radiation therapy on HO in a population with ABI. The authors found that the intervention reduced pain and blood plasma levels of HO markers. Moreover, there were immediate beneficial effects of radiation therapy on range of motion as well as cessation of HO formation post treatment (Lee et al., 2016).

Conclusions

There is level 4 evidence (Lee et al., 2016) that radiation therapy may decrease pain, improve range of motion and prevent further formation of heterotopic ossification in persons with ABI.

KEY POINTS

- Radiotherapy may be effective for the management of pain and range of motion associated with heterotopic ossification in individuals with ABI.

Surgical Interventions

Surgical Excision

Surgical excision of the heterotopic bone is the treatment of choice for those in whom HO has generated marked functional impairment or ulcers in the skin due to deformity (Brady et al., 2018; Moreta & de los Mozos, 2014; Watanabe & Sant, 2001). A recent systematic review found that as many as 55% of those diagnosed with neurogenic HO required surgery (Almangour et al., 2016). Although surgical excision often results in positive outcomes for individuals with HO, severe complications may occur including delayed wound healing, infection, nerve injury and contractures (Ranganathan et al., 2015). Therefore, surgical intervention should be considered only when nonoperative interventions have failed to improve HO (Ranganathan et al., 2015). It has been recommended, based on expert opinion, that surgical

intervention be considered only 12 to 18 months after HO initiation to ensure that the bone tissue has matured and to reduce the likelihood of HO recurrence (Garland, 1991; Sazbon et al., 1981); however, earlier surgical intervention has shown decreased osteopenia and ankylosis, without increased rates of recurrence (Almangour et al., 2016; Genet et al., 2012; Moreta & de los Mozos, 2014). There is some indication that EHDP and nonsteroidal anti-inflammatory medications may be useful in preventing HO recurrence following surgical excision (Watanabe & Sant, 2001); further studies are needed to corroborate this.

TABLE 8 | Surgical Excision for the Management of Heterotopic Ossification post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Pansard et al. (2013) France Case Series N=16	**Population:** TBI=11, Spinal cord injury=2, Stroke=1, Cerebral Anoxia=2; Mean Age=30.1yr; Gender: Male=15, Female=1; Mean Time Post Injury=64mo. **Intervention:** Participants were included in retrospective analysis after receiving surgery for shoulder HO. **Outcome Measure**: Range of Motion (ROM).	1. Mean ROM increased significantly for forward elevation (69°), abduction (60°), and external rotation (13°). 2. Surgical approaches were superolateral (15.8%), deltopectoral (26.3%), posterior (26.3%), posterior-deltopectoral (10.5%), superolateral-deltopectoral (5.3%), axillary (5.3%), and martini (10.5%). 3. No HO recurrence was reported for any of the participants.
Fuller et al. (2013) USA Case Series N=10	**Population:** TBI; Mean Age=30yr; Gender: Male=6, Female=4, Mean Time Post Injury=46.54mo. **Intervention:** Retrospective review of individuals who had resection for restrictive shoulder HO. **Outcome Measure:** Range of Motion (ROM).	1. ROM improved in all 3 planes of motion ($p<0.001$). Specifically, 85°, 59.1° and 66.9° for the sagittal, coronal and axial planes respectively. 2. Three of 11 shoulders had recurrence of HO. One patient developed osteoarthrosis and had avascular necrosis in the opposite shoulder, one had a greater predisposition due to multiple joint involvement, and the other patient had severe post-operative swelling.
Genet et al. (2012) France Case Control N=80	**Population:** TBI; Gender: Male=65, Female=15. *Recurrence Group (n=16):* Mean Age=30.8yr; Mean Time Post Injury=25.3mo. *No Recurrence Group (n=64):* Mean Age=30.3yr; Mean Time Post Injury=31.7mo. **Intervention:** Patients who had surgery for HO (hip, knee, or shoulder) were examined for recurrence. **Outcome Measure:** Recurrence of HO.	1. There was no link between recurrence and timing of surgery (p=0.54). 2. Recurrence was not associated with ABI severity (p=0.81).
Genet et al. (2009) France Case Series N=143	**Population:** TBI=118(hips), Spinal Cord Injury=65(hips); Mean Age=34.5yr; Gender: Male=114, Female=29 **Intervention:** Prospective review of surgical intervention for HO of the hip. **Outcome Measures**: Range of Movement (ROM), surgical complications, pre-operative joint pathology, time from HO diagnosis to surgery	1. Of the 183 hips, 70 had developed ankylosis prior to surgery and 113 had no ankylosis. 2. The mean delay from HO diagnosis to surgery in the ankylosed hips was 34.9mo, compared to 40.8mo in the non-ankylosed hips.

Author Year Country Study Design Sample Size	Methods	Outcome
		3. The mean ROM in ankylosed hips was 0° before surgery, 90° after surgery, and 63° at last follow-up. 4. The mean ROM in non-ankylosed hips was 38° before surgery, 95° after surgery, and 85° at last follow-up. 5. There were no surgical or post-operative complications in the non-ankylosed hips. In the ankylosed hips there were 25 intraoperative femoral neck fractures, leading to 12 total hip replacements, 4 symptomatic non-unions, and 3 deep infections.
Fuller et al. (2005) USA Case Series N=17	**Population:** TBI=15, Anoxia=1, SCI=1; Mean Age=33yr; Gender: Male=10, Female= 7; Mean Time Post Injury=25mo. **Intervention:** A retrospective review of individuals who had surgical excision of HO of the knee. All patients then participated in an inpatient rehabilitation program (e.g., range of motion, passive stretching, weight bearing) and received 20 mg/kg of etidronate disodium for 2mo. **Outcome Measures:** Passive range of motion, Five-level Ambulatory scale, sitting function scale.	1. There was a significant improvement in arc of motion postoperatively (mean 65°, p<0.0001). 2. Extension and flexion significantly improved postoperatively (p<0.002 and p<0.0001, respectively). 3. Significant improvements were found in ambulation and sitting ability postoperatively (both p<0.0001). 4. There were no recurrences of HO by clinical or radiographic examinations at 2, 6, or 12 wk.
Melamed et al. (2002) Israel Pre-Post N=9	**Population:** TBI; Mean Age=38yr; Gender: Male=8, Female=1; Mean Time Post Injury=29mo. **Intervention:** Surgical resection of HO (8 hips, 3 knees, 1 elbow). All patients received postoperative physical therapy and participated in a rehabilitation program. **Outcome Measures:** Functional Status, Range of Motion (ROM), radiographic evaluation, Brooker Classification.	1. The mean preoperative flexion-extension arc of hips was 33°; postoperatively it was 93°. 2. The mean preoperative and postoperative ROM in knees was 58° and 67° respectively. 3. Improved ROM was seen in 7 of 8 hips; 4 patients had marked improvement in gait, 2 of whom no longer required prosthetics. 4. For follow-up (n=8), 7 graded themselves as functionally improved and 7 reported improved ROM.
de Palma et al. (2002) Italy Case Series N=10	**Population:** TBI; Mean Age=Not Reported; Gender: Male=6, Female=4; Mean Time Post Injury=Not Reported. **Intervention:** Surgical resection of HO of the elbow with Indomethacin (25 mg, 3x/day for 6 wk) administered postoperatively. Active mobilization of the elbow joint commenced 1 mo after surgery. **Outcome Measures:** Garland's Classification, Range of Motion (ROM).	1. All patients had improved ROM in the early postoperative period, especially those who had the most severe preoperative restriction in joint mobility. 2. Improvement correlated with residual neurological damage. Class I and II (minimal physical/cognitive benefits) patients had the greatest improvements, achieving satisfactory ROM, while class III (more marked physical deficits) had only partial improvement in ROM.

Author Year Country Study Design Sample Size	Methods	Outcome
Lazarus et al. (1999) USA Pre-Post N=24	**Population:** TBI; Mean Age=37.4yr; Gender: Male=20, Female=7; Mean Time Post Injury=35.4mo. **Intervention:** Patients had HO resection in a total of 27 elbows. All patients received indomethacin (25-50 mg, 2x/day) after surgery. Some patients (n=17) received continuous passive motion. **Outcome Measure:** Range of Motion (ROM).	1. Maximum flexion increased from 80.1° preoperatively to 111.9° postoperatively (p=0.0003). 2. Maximum extension increased from 58.9° preoperatively to 32.1° postoperatively (p=0.0005). 3. Twenty-three elbows gained motion and 4 lost a mean of 15°. 4. The patients with ankylosed elbows (n=17) preoperatively, made greater gains than the remaining patients (n=10), demonstrating mean gains of 59.1° vs 23.2° (p=0.03). 5. Patients with longer injury to resection times had worse outcomes compared to those with shorter times (p=0.02). 6. Patients who had continuous passive motion after surgery had greater ROM gains than those who did not (57.9° vs 24.1°, p=0.04).
Ippolito et al. (1999a) Italy Case Series N=12	**Population:** TBI; Mean Age=29yr; Gender: Male=9, Female=3. **Intervention:** Surgical resection of hip HO (total of 13 hips). As an antibiotic prophylaxis, each patient received Cefazolin (800 mg, 3x/day for 2 wk). Indomethacin (50 mg, 2x/day for 6 wk) was also given after the operation. **Outcome Measures:** Walking capacity, hip range of motion (ROM).	1. All patients showed satisfactory ROM following the surgery. 2. Radiographs revealed remnants of HO following surgery; these remnants did not interfere with ROM. 3. At final follow up (mean 38 mo post-operatively), 8 hips maintained initial gains in ROM, 2 had decreased ROM with no evidence of HO recurrence and 3 decreased ROM with partial or full recurrence of HO. 4. All patients who had a painful hip prior to operation (n=5) were pain free after. 5. Nine of 12 patients were non-ambulatory prior to surgery; post-operatively, 10/12 were able to ambulate (5 with braces or crutches).

Author Year Country Study Design Sample Size	Methods	Outcome
Ippolito et al. (1999b) Italy Case Series N=14	**Population:** TBI; Mean Age=30.8yr; Gender: Male=10, Female=4. **Intervention:** Surgical resection of HO in 16 elbows. Immediately after the surgery, a continuous passive motion machine was applied and was gradually increased until the joint regained the whole arc of motion (6wk). Patients assigned to one of two groups. Group 1: elbows ankylosed in position (ranged from 0-100°; n=11 elbows) or group 2: elbows in which 10–25° of flexion was available (n=5 elbows). **Outcome Measure:** Arc of elbow range of motion (ROM).	1. At the end of surgery, the arc of flexion attained ranged from 90-145° in group 1 and 115-140° in group 2. 2. At follow up (mean 30.7 mo), the arc of flexion (both active and passive) attained ranged from 30-135° in group 1 and 80-145° in group 2. 3. 9 joints lost ROM, 3 joints gained ROM and 4 joints retained the same ROM at follow-up, relative to post operation. 4. Partial recurrence was observed in 3 elbows. 5. The average arc of flexion for those who had surgery <18 mo (n=11) or >18mo (n=5) after coma, was 105° and 92°, respectively.
Ippolito et al. (1996c) Italy Case Series N=5	**Population:** TBI; Mean Age=26yr; Gender: Male=3, Female=2. **Intervention:** Patients had surgical resection of HO in 7 knees. Post-surgery, a continuous passive motion machine was applied and used daily until the joint had regained the whole arc of motion that was seen at time of operation (approximately 6 wk). **Outcome Measures:** Arc of knee motion, recurrence of HO.	1. At baseline, all knees were in a fixed flexed position (10-40°) with a painful arc of motion (20-70°). 2. At follow up (mean 34 mo) the arc of motion had improved in all of the knees (0–130° in 3 knees, 0–120° in 3 knees, and 10–120° in 1 knee). 3. At follow up, arc of flexion was 10-100° for 2 patients, 0-120° for another 2 patients, and 0-90°, 5-110°, and 0-130° for the remaining 3 patients. 4. None of the patients could walk before the operation; however, at follow up, all patients could walk, and all knees were pain free. 5. Ossification did not recur in any of the knees.
Charnley et al. (1996) France Case Series N=5	**Population:** TBI; Mean Age=28.4yr; Gender: Male=5, Female=0; Mean Time Post Injury=Not Reported. **Intervention:** Patients underwent surgical excision of HO around the knee (total of 7 knees). Postoperatively, all patients underwent early rehabilitation to maintain function and were given indomethacin to prevent recurrence of HO. **Outcome Measures:** Range of Motion (ROM), recurrence of HO.	1. At follow up (mean 18mo) there was no delayed wound healing or recurrence of HO around the knee. 2. All patients had significant pain relief and improved ROM. 3. Overall benefit meant patients could lie in bed as well as sit and transfer with greater ease and comfort

Author Year Country Study Design Sample Size	Methods	Outcome
Kolessar et al. (1996) USA Case Series N=17	**Population:** TBI; Mean Age=35yr; Gender: Male=14, Female=3; Mean Time Post Injury=30mo. **Intervention:** Retrospective review of surgical excision of HO (24 procedures: 11 hips, 10 elbows, 3 knees). Post operatively patients received Indomethacin (min. 75mg/d) and Etidronate (20mg/kg/d) for approximately 3mo. Physical therapy was also provided. **Outcome Measures:** Range of Motion (ROM), recurrence of HO, ambulation.	1. The mean improvement in motion for the hips, elbows and knees were 73.2°, 75.7°, and 52.6°, respectively. 2. Of 21 cases with radiographic follow-up, recurrence of HO was found in 23.8% based on the Brooker classification or 4.8% based on the Stover and colleague classification. 3. 91.3% participants were satisfied with the functional outcome. 4. Functional goals were achieved by 83.3% of the sample and improvements in ambulation were found in 75% of patients.
Moore (1993) USA Case Series N=17	**Population:** TBI; Mean Age=26yr; Gender: Male=17, Female=0; Mean Time Post Injury to Surgery=21mo. **Intervention:** Retrospective study of patients who had surgical excision of HO (13 hips, 7 elbows). Patients received etidronate disodium (10 mg/kg per day for approximately 3mo) post-surgery. **Outcome Measure:** Range of Motion (ROM).	1. The average arc of motion obtained immediately after surgery was 85° for the hips and 65° for the elbows. 2. Eleven hip joints and 6 elbow joints maintained sufficient ROM to achieve pre-operative functional goals (e.g., enhanced wheelchair sitting, improvement in bed to wheelchair transfers or improvements in activities of daily living). 3. Three of 20 joints had recurrence of HO.

Discussion

Fourteen studies examined the effects of surgical excision of HO. Two studies focused on the shoulder (Fuller et al., 2013; Pansard et al., 2013) three on the elbow (Almangour et al., 2016; de Palma et al., 2002; Ippolito, Formisano, et al., 1999b; Lazarus et al., 1999), two on the hip (Genet et al., 2009; Ippolito, Formisano, et al., 1999a), three on the knee (Charnley et al., 1996; Fuller et al., 2005; Ippolito, Formisano, Farsetti, et al., 1999) and three studies examined more than one type of joint (Kolessar et al., 1996; Melamed et al., 2002; Moore, 1993).

Overall, the surgical excision of HO resulted in improvements in range of motion; however, one study did note a decrease in range of motion for a small portion of participants (Ippolito, Formisano, et al., 1999a). Improvements in activities of daily living and ambulation were also found (Fuller et al., 2013; Fuller et al., 2005; Ippolito, Formisano, et al., 1999a, 1999b; Melamed et al., 2002). Improvements in functional outcomes after surgical excision have also been reported in several reviews (Almangour et al., 2016; Brady et al., 2018; Genet et al., 2011).

De Palma et al. (2002) found that range of motion improvement was correlated with level of neurological damage, with lesser damage correlating with improved outcomes. It is also worth noting that length of time between injury and surgical resection was found to be a significant predictor of outcome, as longer

times were associated with less improvement (Lazarus et al., 1999). Additionally, Genet et al. (2009) found progression of HO to ankylosis of the hip lead to non-use and osteopenia, which increased perioperative complications.

Only one study formally evaluated the effectiveness of physical rehabilitation therapy after surgery. The authors found that patients who had continuous passive motion exercises post operatively made significantly greater gains those individuals who did not (Lazarus et al., 1999).

In several studies, the recurrence of HO was evaluated months following the initial operation, with rates ranging from 0 to 27% (Fuller et al., 2013; Fuller et al., 2005; Genet et al., 2012; Ippolito, Formisano, et al., 1999b; Ippolito, Formisano, Farsetti, et al., 1999; Kolessar et al., 1996; Moore, 1993; Pansard et al., 2013). However, variability of study protocol (e.g., follow-up schedules, post-operative management) makes comparisons of recurrence rates difficult. For example, the prophylactic treatments used in the literature include indomethacin (Charnley et al., 1996; de Palma et al., 2002; Ippolito, Formisano, et al., 1999a; Lazarus et al., 1999), etidronate disodium (Fuller et al., 2005; Moore, 1993), radiotherapy (Fuller et al., 2013; Melamed et al., 2002), a combination (Genet et al., 2012; Kolessar et al., 1996), or physiotherapy alone (Genet et al., 2009; Pansard et al., 2013). In addition, the majority of the studies did not specify what qualified as recurrence.

In a systematic review, Almangour et al. (2016) examined recurrence of HO after surgical excision in patients with TBI and found that estimations of recurrence rates varied widely (5.6% - 58%) based on radiographic, clinical, or surgical definitions of recurrence. The authors found no relationship between timing of surgery, preoperative extent of HO, or severity of neurological sequelae and incidence of recurrence (Almangour et al., 2016). This was consistent with the findings of Genet et al. (2012) and another systematic review by Chalidis et al. (2007), where there was no relationship between timing of surgery and recurrence. Therefore, surgical excision was recommended as soon as comorbid factors are controlled (Almangour et al., 2016). In another systematic review, Lee et al. (2013) focused specifically on the surgical excision of HO in the elbow and found improvements in motion with low levels of recurrence (14.3%). However, complications such as fracture, infection and nerve palsies were found in 27.5% of cases (Lee et al., 2013).

Conclusions

There is level 3 evidence (Genet et al., 2012) that early surgical excision may not increase the recurrence risk of heterotopic ossification compared to delayed surgical excision.

There is level 4 evidence (Fuller et al., 2013; Genet et al., 2009; Fuller et al., 2005; de Palma et al., 2002; Ippolito et al., 1999a; Ippolito et al., 1999b; Ippolito et al., 1999c; Charnley et al., 1996; Kolessar et al., 1996; Moore et al., 1993; Melamed et al., 2002; Lazarus et al., 1999) that surgical excision may improve range of motion and functional outcomes in ABI populations with heterotopic ossification.

KEY POINTS

- Surgical excision may improve range of motion and functional outcomes in ABI populations with heterotopic ossification.
- Early surgical excision may not increase the risk of recurrent heterotopic ossification.

Conclusion

Given that heterotopic ossification often results in significant disability, poor quality of life and significant morbidity in individuals with brain injuries, there is a need for more research on both prophylactic and management interventions for this condition. While surgery is the most frequently used intervention, prophylactic interventions are limited and not well studied (Rizvi et al., 2022). In addition, more research is needed to properly understand which individual factors may predict the formation of HO and contribute to recurrence (Meyers et al., 2019).

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