8. Heterotopic Ossification & Venous Thromboembolism

On behalf of the ERABI Research Group

Definition of Heterotopic Ossification

Q. What is heterotopic ossification?

Answer

- Process whereby true lamellar bone forms ectopically within tissues where bone formation does not usually occur.

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). The incidence of HO in patients with traumatic brain injury (TBI) has been reported to range from 11–77% but is clinically relevant in 10–20% (Dizdar et al. 2013; Garland et al. 1980; Rogers 1988; Sarafis et al. 1999; Sazbon et al. 1981). Risk factors include skeletal trauma, spasticity, diffuse axonal injury, mechanical ventilation, prolonged immobilization, and injury severity (Moreta & de los Mozos 2014). HO is often quite painful and limits joint mobility; the restricted joint range of motion (ROM) may exacerbate disability and impede progress towards desired rehabilitation goals.

8.1 Formation of Heterotopic Ossification Post Head Injury

Pathophysiology of Heterotopic Ossification Post Head Injury

Q. Describe the pathophysiology of heterotopic bone formation post ABI.

Answer

- Pathophysiology of heterotopic ossification is not well understood; it is believed that there is a neurogenic factor (e.g. mesenchymal stem cells) contributing to the development of heterotopic ossification.
- Initially there is formation of osteoid periarticularly and intramuscularly.
- There is progression to full calcification within weeks.
- Calcified osteoid remodels into well-organized mature trabecular bone over months.
- In heterotopic ossification, the bony lesion has been found to have a high metabolic rate. The rate of bone formation is more than three times that of normal bone and there are more than twice the number of osteoclasts present when compared with normal bone.

The pathophysiology of HO has not been comprehensively established. It is believed that there is a neurogenic factor contributing to HO, although this mechanism is not yet fully understood (Antiplatelet Trialists' Collaboration 1994; Hurvitz et al. 1992; Pape et al. 2001; Pape et al. 2004). It has been noted that mesenchymal stem cells can generate cartilage, bone, muscle, tendons, ligaments or fat (Pape et al.

2004) and are thought to play a pivotal role in the development of HO (Williams et al. 1999). Pape et al. (2004) have noted that circulating factors promoting HO may be present in patients with brain injury. Trentz et al. (2005) have noted that many studies have shown enhanced osteogenesis in patients sustaining TBI. The presence of certain hormonal factors early post injury influences the stimulation of osteoprogenitors within skeletal muscles (Ivanhoe et al. 2012). 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 patients with brain injury (Bidner et al. 1990; Keret et al. 1990).

HO forms through a typical process beginning with the formation of osteoid periarticularly and intramuscularly, and progresses to full calcification within a matter of weeks (Pape et al. 2001). 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 initial trauma, patients with HO begin to experience restricted ROM, pain and 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).

8.2 Clinical Presentation of Heterotopic Ossification

Location of Lesion

Q. Which joints are most often involved in heterotopic ossification post TBI?

Answer

- Most commonly affected joints are the hip, then shoulders, elbows and rarely the knee.

Among individuals with TBI the most commonly sites of HO are the soft tissues around the hip, elbow, shoulder and knee (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 a head 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 head injury, ankylosis is most likely to occur in the posterior elbow (Garland et al. 1980).

Clinical Features

Q. Describe the clinical picture of heterotopic ossification post ABI.

Answer

- Clinical features of heterotopic ossification include a warm, swollen and painful joint often associated with decreased range of motion.

Pape and colleagues (2004) noted that clinical examination in the setting of HO may reveal a swollen, warm, painful joint which is often associated with a decreased range of motion. The earliest sign is typically a loss of range of motion in the involved joint (Watanabe & Sant 2001). Other findings then include erythema, palpation of a peri-articular 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 venous thrombosis (DVT), local trauma or fracture (Buschbacher 1992; Jensen et al. 1987). The timing of onset of HO has been reported to vary between 2 and 3 weeks post injury (Watanabe & Sant 2001) and 1 and 7 months post injury (Sazbon et al. 1981). More recently, clinical signs and symptoms have been said to develop 3-12 weeks post injury (Vanden Bossche & Vanderstraeten 2005).

Diagnostic Testing for Heterotopic Ossification

Q. Describe which tests can be helpful in diagnosing heterotopic ossification post TBI?

Answer

- Plain radiographs are negative, and remain negative, until ossification occurs 4–6 weeks post injury.
- Serum levels of alkaline phosphatase and the erythrocyte sedimentation rate may become elevated early on but are non-specific.
- Triple phase technetium-99 bone scan with increased uptake during the first and second phases remains the gold standard, becoming positive at about the same time as clinical features appear.

The triple phase technicium-99 bone scan remains the diagnostic gold standard. The test is positive if there is an increased uptake during the first and second phases of the study. It typically becomes positive when clinical features appear (i.e. before an x-ray would be positive).

8.3 Interventions for Heterotopic Ossification Post ABI

Q. What prophylactic treatment options are available for heterotopic ossification post ABI?

Answer

- Physiotherapy/range of motion exercises
- Forceful manipulation under general anesthesia
- Nonsteroidal anti-inflammatory medications
- Low-dose radiation
- Disodium Etidronate

Physiotherapy and Range of Motion Exercises

At one time, the literature on ROM therapy post acquired brain injury (ABI) suggested that such experiences actually contributed to the development of HO (Chantraine & Minaire 1981; Crawford et al. 1986). A shift in thinking practice then occurred towards the utilization of ROM exercises, and even joint manipulation under anaesthesia, to help prevent ankyloses in patients with ABI (Garland 1991; Garland et al. 1982). Pape et al. (2004) have noted that for HO careful and judicious use of physiotherapy, involving assisted ROM exercises and gentle stretching, has been shown to be of benefit (Ellerin et al. 1999). However, it has been cautioned that care should be taken not to move the joint beyond its pain-free ROM as this can exacerbate the condition (Evans 1991; Pape et al. 2004).

Garland et al. (1982) conducted a review of TBI patients who underwent forceful manipulation of joints with pre-existing HO under anesthesia and reported that it was useful in maintaining and increasing range of motion. With 82% of joints having increased range of motion, the authors concluded that forceful manipulation is not only useful in maintaining motion but also aids in the prevention of bony ankylosis and did not appear to exacerbate the ossification process (Garland et al. 1982; Garland & Varpetian 2003). Garland and Varpetian (2003) also noted that patients with ABI frequently suffer from spasticity, intolerance to pain and voluntary muscle guarding. As a result, anaesthesia may be needed to help differentiate between spasticity and ankylosis and to allow sufficient muscle relaxation to perform the joint manipulation (Garland & Varpetian 2003).

Continuous Passive Motion

Continuous passive motion devices have shown promising results in maintaining ROM following total knee replacement (Nadler et al. 1993; Salter 1996). Animal data shows that continuous passive motion does not increase the progression of HO (van Susante et al. 1996). Moreover, there is little human research evidence that HO is worsened by passive ROM (Linan et al. 2001). Although it may help postoperatively, further research is needed in the post ABI population.

Nonsteroidal Anti-Inflammatory Medications

The evidence for nonsteroidal anti-inflammatory medications as prophylactic treatment for HO comes mostly from the use of indomethacin or ibuprofen as HO prophylaxis in patients following total hip arthroplasty (Kjaersgaard-Andersen & Schmidt 1986; Ritter & Sieber 1985). Although it has been noted

that prophylactic use of these medications offer a significant decrease in the formation of HO following total hip arthroplasty, it is not known if they have the same effect in the post ABI population.

Disodium Etirdronate

Watanabe and Sant (2001) have noted that the use of bisphosphonates, in particular EHDP, for the prophylaxis and treatment of HO is controversial. EHDP works by preventing the aggregation, growth and mineralization of calcium hydroxyapatite crystals which are essential for bone formation. EHDP may potentially delay fracture healing, as long-term use has been associated with osteomalacia. Although EHDP has been shown to be effective in reducing HO in other populations, such as spinal cord injury (SCI), its effectiveness among individuals with brain injury is less studied. In an ABI population, Spielman et al. (1983) did find that patients treated with EHDP showed a significantly lower incidence of HO than the control group. However, due to the small sample size of the study (n=20) and the research design (i.e. cohort), additional research assessing the benefit of EHDP for the treatment of HO following brain injury is needed.

Surgical Excision

Q. Does surgical excision of heterotopic ossification post ABI improve clinical outcomes?

Answer

- There is Level 4 evidence that surgical excision of heterotopic ossification improves clinical outcomes.

Surgical excision of the heterotopic bone has been suggested as a possible option for those in whom HO has generated marked functional impairment or ulcers in the skin due to deformity (Watanabe & Sant 2001). It had been suggested, based on expert opinion, that surgical treatment should be considered only 12–18 months after HO onset to ensure that the bone tissue has matured, and to reduce the likelihood of recurrence (Garland 1991; Sazbon et al. 1981), although the issue of timing is controversial and has changed in recent years (Moreta & de los Mozos 2014).

A systematic review by Lee et al. (2013) focused specifically on the surgical excision of HO in the elbow and found it resulted in improvements in motion, with low levels of recurrence (14.3%). However, complications such as fracture, infection, nerve palsies, wound complications and loss of motion without recurrence were found in 27.5% of cases (Lee et al. 2013).

There is some indication that EHDP and nonsteroidal anti-inflammatory medications may be useful in preventing HO recurrence following surgical excision (Watanabe & Sant 2001), although further studies are still needed to corroborate this claim. Watanabe and Sant (2001) have reported that recurrence of HO following surgical excision usually occurs within 3 months post operation. In many studies, the recurrence of HO was evaluated months following the initial operation, with rates ranging from 0–27% (Fuller et al. 2013; Fuller et al. 2005; Ippolito et al. 1999a, 1999b; Ippolito et al. 1999; Moore 1993). Kolessar et al. (1996) found recurrence rates differed based on the classification system utilized (23.8% versus 4.8% using the Brooker classification and the Stover and colleagues classification, respectively).

Overall, the surgical excision of HO resulted in improved range of motion. One study did note a decrease in range of motion for a small portion of participants (Ippolito et al. 1999a). Improvements in activities of daily living and ambulation were also found (Fuller et al. 2005; Ippolito et al. 1999a; Ippolito et al. 1999; Melamed et al. 2002). It is 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). Although therapy was provided after the surgery in many of the studies, only one study formally evaluated its effectiveness. The study conducted by Lazarus et al. (1999) found that patients who had continuous passive motion exercises post operatively made significantly greater gains those individuals who did not (57.9° versus 24.1°, p=0.04).

Heterotopic Ossification Recommendations (ABIKUS Guidelines; Bayley et al. 2007)

G75 (p. 28)
The interdisciplinary team should be aware of the possibility of heterotopic ossification and protocols should be in place for early detection and management including:

- The use of three-phase bone scans to detect active areas of heterotopic ossification.
- The early use of disodium etidronate 30 mg/kg/day for 2 months and/or nonsteroidal anti-inflammatory drugs to limit evolution of heterotopic ossification.
- Surgical excision should be considered at a later stage if the limitation in joint motion hinders the patient's rehabilitation. (ABIKUS B, adapted from RCP, G62, p. 31–32)

G76 (p. 28)
Forceful manipulation of joints under general anaesthesia increases range of motion in patients with heterotopic ossification following brain injury. (ABIKUS B)

Venous Thromboembolism

Venous thromboembolism (VTE), including DVT and pulmonary embolism (PE), remains a common complication in patients who have sustained an ABI (Raslan et al. 2010; Scudday et al. 2011). However, the scientific literature pertaining specifically to the ABI population is quite limited.

8.5 Incidence of Venous Thromboembolism Post Head Injury

Q. What is the incidence of deep venous thrombosis post TBI?

Answer

- The incidence of deep venous thrombosis post TBI ranges from 11–54%

The reported incidence of DVT among patients with TBI ranges from 11–54% (Carlile et al. 2010; Cifu et al. 1996; Denson et al. 2007; Geerts et al. 1994). Furthermore, according to a recent study by Haddad and Arabi (2012), the risk of developing a DVT or PE, in the absence of prophylaxis, is estimated to be approximately 20% post TBI.

8.6 Risk Factors for Deep Venous Thrombosis

Q. What are the three elements of Virchow's triad?

Answer

- Venostasis
- Intimal damage of the vessel wall
- Hypercoagulability

Watanabe and Sant (2001) have noted that the most recognized risk factors for VTE are venostasis, intimal damage of the vessel wall, and a hypercoagulable state, collectively known as the Virchow's triad. Patients with a severe brain injury are commonly immobilized for periods of time as a result of extremity or spine fractures they experienced at the time of their injury (Vergouwen et al. 2008).). The incidence of DVT appears to be impacted by length of stay in the ICU and the number of days a patient is on a ventilator. There does not appear to be a correlation between DVT incidence and initial GCS, Injury Severity Scale scores, or the Abbreviated Injury Scale score (Denson et al. 2007). Those at highest risk post injury are those who remain on a ventilator longer than three days (Raslan et al. 2010). Patients involved in trauma that does not specifically involve vessel injury are still at increased risk of thromboembolism, suggesting a trauma-induced hypercoagulable state (Geerts et al. 1994; Geerts et al. 1996).Therefore persons who have sustained a TBI appear to be at increased risk of developing VTE.

8.7 Clinical Presentation of Deep Venous Thrombosis and Pulmonary Embolism Post ABI

The clinical presentation of DVT varies depending on the severity. Signs and symptoms may include pain, swelling, tenderness, skin discolouration and increased warmth of the affected area. The clinical presentation of PE is challenging. Many cases are clinically silent (66%) with only 30% having the clinical features of a DVT (Garcia-Fuster et al. 2014). Asymptomatic PE is discovered in 70% of patients with confirmed clinically symptomatic DVT (Browse 1974; Corrigan et al. 1974; Hull & Hirsh 1983). Clinically, PE presents with tachycardia, tachypnea and signs of pulmonary infarction with consolidation, hemoptysis, pleuritic chest pain, pleural friction rub, pleural effusion and fever (Worku et al. 2014). Massive PE may cause right heart failure, which can progress to cardiovascular collapse, coma and death.

8.8 Diagnostic Testing for Deep Venous Thrombosis and Pulmonary Embolism Post ABI

Diagnosis of Deep VenousThrombosis

A positive diagnosis of DVT can only be made if a venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. The diagnosis of DVT can be ruled out if there is a negative venogram, a negative d-dimer test or a normal venous ultrasound assuming the venous ultrasound is accompanied by one of the following findings: 1) low clinical suspicion for DVT, 2) normal d-dimer test, or 3) negative serial ultrasound performed one week later. In an email survey 56% of respondents from acute centers reported the use of venous duplex ultrasonography (VDU) to screen for DVTs post ABI, whereas 13% rehabilitation hospital responders use D-dimer along with VDU for routine screening of DVT post injury (Carlile et al. 2006).

Venous Ultrasound

Venous ultrasound is often used to diagnose a DVT. There are several types of venous ultrasonography. They include compression ultrasound, duplex ultrasound and color Doppler imaging. Although these types of venous ultrasonography are sometimes used interchangeably, their sensitivities and specificities for detecting acute DVT vary (Zierler 2004). The sensitivity and specificity of compression ultrasonography for detecting DVTs is 43% and 85%, respectively (Girard et al. 2005). The weighted mean sensitivity and specificity of venous ultrasonography for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively; the sensitivity falls to 73% for distal DVTs (Kearon et al. 1998; Zierler 2004). Importantly distal DVTS do not confer the same risk of extension to PE as do Proximal DVTs. Typically, if a distal clot is going to extend proximally, this occurs within one week of its development. Consequently, serial ultrasound could be used in symptomatic patients in whom the test is initially negative as the test would become positive with the clot extension.

Venography

Venography is considered a definitive test for DVT but it is an invasive test whereby contrast dye is injected into the leg veins. Diagnosis of DVT is made if an intraluminal-filling defect is noted.

D-dimer Assay

D-dimer assay is a rapid, non-invasive and inexpensive test. Fibrin is the main component of thrombus formation—fibrin degradation products include D-dimers (Gill & Nahum 2000). A positive D-dimer test is highly sensitive for the presence of a thrombus but lacks specificity since D-dimers are found in other disease states, including cancer, congestive heart failure and inflammatory conditions (Raimondi et al. 1993). As a result, D-dimer assays have a high negative predictive value but a poor positive predictive value. To illustrate, Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-dimer test were high, at 95.2% and 96.2%, respectively, in a group of 68 patients rehabilitating from stroke, SCI, TBI, or hip arthroplasty. The specificity and positive predictive values were low, at 55.3% and 48.7%, respectively.

Ventilation/Perfusion Scanning

Nuclear ventilation/perfusion scans are often used to investigate possible PE. Palmowski et al. (2014) reported the sensitivity and specificity of ventilation/perfusion scanning as 95.8% and 82.6%, respectively, with false negative rates of 4.2% and false positive rate of 17.3%. Hence, a normal scan virtually excludes a PE (high negative predictive value). Identified perfusion defects are non-specific and only represent true PE in about one-third of cases. The probability that a perfusion defect represents a PE increases with the size, shape and number of defects as well as the presence of a normal ventilation scan. When clinical suspicion is high and the scan indicates a high probability of PE, the positive predictive value is 96% (Gill & Nahum 2000; PIOPED Investigators 1990), and these patients should be treated. The majority of ventilation perfusion scans have non-diagnostic results, requiring further testing (PIOPED Investigators 1990).

Pulmonary Angiography

Pulmonary angiography is the gold standard for diagnosis of PE (Gill & Nahum 2000). It involves percutaneous catheterization and injection of contrast dye into a pulmonary artery branch (Gill & Nahum 2000). Pulmonary angiography is most commonly used when ventilation-perfusion scanning is non-diagnostic but clinical suspicion remains high (Tapson et al. 1999). A negative pulmonary angiogram excludes clinically relevant PE (Gill & Nahum 2000; Tapson et al. 1999). It is expensive and is associated with the risk of significant complications. Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum 2000).

Spiral Computed Tomography Scan

A spiral computed tomography (CT) scan is a non-invasive test, which can scan the entire thorax in one breath-hold. The sensitivity of spiral CT in diagnosing PE has been reported to range from 64–93%, with a specificity ranging between 89–100% (Katsouda et al. 2005; Righini et al. 2008). Whilst it has the benefit of investigating other manifestations of PE, spiral CT scanning is less accurate with smaller emboli (Katsouda et al. 2005).

8.9 Prophylaxis of Deep Venous Thrombosis Post ABI

To date, the recommendation for treating those who sustain a DVT post ABI is the administration of medication (Elliott et al. 2006; Scudday et al. 2011); however there is no agreement for the administration of these medications in terms of timing, dose, and the specific medication.

Mechanical Interventions to Prevent Deep Venous Thrombosis Post ABI

Mechanical interventions used to prevent the development of DVT post ABI include: the insertion of vena cava filters, thromboembolism deterrent stocking, intermittent pneumatic compression devices including arteriovenous foot pumps and sequential compression devices (SCDs). These devices operate primarily through two distinct mechanisms of action. The first is mechanical, in which the device increases the velocity of venous return to decrease venous stasis; the second, and perhaps more important, mechanism involves the systemic activation of the fibrinolytic system, which during compression, leads to the breakdown of fibrin clots associated with thromboembolism (Macatangay et al. 2008). Another method of mechanical DVT prevention is the vena cava filter (Watanabe & Sant 2001). These filters are inserted into the inferior vena cava to prevent the passage of distal emboli into the lungs. Some reports have demonstrated success rates as high as 96% in the prevention of PE (Greenfield & Michna 1988). However, the use of vena cava filters is associated with some risk. For instance the filters can become blocked or dislodged, increasing the risk of an embolism. Some have also reported increased risks for recurrent DVT in patients with vena cava filters compared with patients without such devices (Decousus et al. 1998).

Q. What is the evidence for using mechanical interventions in the prophylaxis of deep venous thrombosis post ABI?

Answer

- There is Level 2 evidence that sequential compression devices are not entirely effective in reducing the risk of developing deep venous thrombosis or pulmonary embolism post ABI.
- There is Level 4 evidence that intermittent compression devices do not cause acute elevations in intracranial pressure in patients with severe ABI.

In a cohort study comparing clinical outcomes of patients either receiving or not receiving prophylaxis (e.g. SCDs), the authors found that groups did not differ significantly in the development of DVT or PE (Gersin et al. 1994). Of 32 patients admitted to the surgical intensive care unit with severe TBI, a total of eight patients developed DVT or PE following injury, half of whom had received prophylactic SCDs. The effectiveness of prophylactic SCDs in the prevention of post-TBI DVT or PE thus remains questionable.

In an earlier pre-post study, Davidson et al. (1993) investigated whether intermittent pneumatic compression devices aggravate intracranial hemodynamics in patients with severe brain injuries. The authors reported that the use of intermittent compression devices to prevent the occurrence of DVT was not associated with any significant changes in intracranial pressure or cerebral perfusion pressure in stable patients in whom intracranial pressure was controlled by conventional measures (Davidson et al. 1993). These findings suggest that there is no contraindication to the use of pneumatic compression for the prevention of DVT in severe acute patients with brain injury who are responsive to conventional intracranial management measures.

Pharmaceutical Therapies

Oral agents have been investigated for their prophylactic potential against DVT. Warfarin (Coumadin), a well-established anticoagulant with a predictable duration of action, is sometimes avoided as a prophylactic alternative for DVT due to its elevated bleeding side effects (Watanabe & Sant 2001). However, some experts felt the use of warfarin was advisable, especially for high risk patients due to its benefit in treating undetected thrombosis; the therapeutic concentration for prophylaxis and treatment of thromboembolism are the same (Hirsh et al. 1992; Hyers et al. 1992; Landefeld & Goldman 1989). In a recent study with a sample of 932 patients, 71% were given low-molecular weight heparin (LMWH), 23% heparin, 1% Coumadin, and 3% were given both LMWH and low-dose unfractionated heparin (LDUH), none of which were associated with increased intracranial or systemic hemorrhage (Carlile et al. 2010). The most recent guidelines on DVT prophylaxis recommend using LMWH or LDUH in addition to mechanical prophylaxis (Elliott et al. 2006; Reiff et al. 2009). There is also evidence from a meta-analysis, that aspirin has positive effects in the reduction of both DVT and PE by 40% and 60%, respectively (Antiplatelet Trialists' Collaboration 1994). Clinically there remain concerns that chemical DVT prophylaxis may result in increased intracranial bleeding post ABI. Overall there is a lack of persuasive evidence to guide decisions about when to administer anticoagulant prophylaxis in those who sustain traumatic intracranial hemorrhage. Clinicians often make decisions based on their own assessments of the risks and benefits (Scales et al. 2010). To date no national standard of care exists for the administration of the pharmacological prophylaxis treatment of DVT post TBI (Phelan et al. 2012).

Q. What is the evidence for using heparin in the prophylaxis of deep venous thrombosis post ABI?

Answer

- There is Level 2 evidence supporting the administration of low-molecular weight heparin within the first 72 hours post ABI to reduce the risk of developing deep venous thrombosis and pulmonary embolisms post injury.
- There is Level 2 evidence that administering low-molecular weight heparin (enoxaparin) or heparin post ABI does not increase the risk of intracranial bleeding.
- There is Level 4 evidence that the use of chemoprophylaxis 24 hours after stable head computed tomography decreases the rate of deep venous thrombosis formation post ABI.

The effect of administering chemical prophylaxis for DVT post ABI has been reviewed. In recent studies, results indicate that early treatment (within 72 hours of injury) may reduce the risk of developing DVTs post injury (Farooqui et al. 2013; Kim et al. 2002; Norwood et al. 2008; Salottolo et al. 2011; Scudday et al. 2011) without increasing the risk of intracranial hemorrhagic injury (Koehler et al. 2011; Scudday et al. 2011) or deterioration on neurological examination (Kim et al. 2002).

In a retrospective study, Kim et al. (2002) looked at differences between patients with ABI, who were started on unfractionated heparin within 3 days of injury onset or after this time period. The findings showed no statistically significant differences between the groups in the number of thromboembolic events. Norwood and colleagues conducted two studies examining the benefits of administering enoxaparin prophylaxis to those who sustain a severe ABI within 24–48 hours post injury (Norwood et al. 2008; Norwood et al. 2002). Results from both studies indicate that administering enoxaparin post ABI reduces the risk of developing DVTs and PEs, without increasing the risk of bleeding post injury. Scudday et al. (2011) also found that patients who received chemical prophylaxis within 72 hours of injury had a significantly lower incidence of developing VTE post ABI ($p<0.019$) compared to those not receiving chemical prophylaxis. However, Kwiatt et al. (2012) reported patients receiving LMWH were at higher risk for hemorrhage progression and the risk of using LMWH may exceed its benefit.

Despite these studies, there remains no definitive answer regarding when to administer these medications post ABI. The Brain Trauma Foundation guidelines recommend using chemical prophylaxis (LMWH or heparin) until the patient is ambulatory (Elliott et al. 2006); however, injuries to the lower extremities would impact upon this. There is a need for quality controlled studies in this area.

Subcutaneous Heparin

Subcutaneous heparin in low doses has been reported to be both safe and effective as prophylaxis against DVT development post ABI (Watanabe & Sant 2001). The route of delivery may also affect the efficacy of anticoagulant prophylaxis (Watanabe & Sant 2001). For this reason, intravenously delivered heparin may be more effective in the prevention of thromboembolism compared with subcutaneous administration, although this method of delivery might increase the risk of bleeding (Green et al. 1988). LMWHs, which are injected subcutaneously, have gained popularity due to the ease of administration and dosage adjustment. Of note, low-molecular weight variants of unfractionated heparin are significantly more expansive, and thus the risks, benefits, and costs need to be balanced out on an

individual basis (Watanabe & Sant 2001). Carlile et al. (2006) found that 15 of the 16 rehabilitation centers surveyed reported routinely initiating treatment with either LMWH or LDUH. In a study with a mixed trauma population, low-dose heparin was compared to enoxaparin for the treatment of DVT (Geerts et al. 1996). Of those receiving low-dose heparin 44% sustained a DVT compared to 31% of patients receiving enoxaparin (p=0.014; Geerts et al. 1996).

Combination Interventions

Compression stockings and pneumatic compression devices are the major strategies used for the prevention of DVT in patients with TBI (Watanabe & Sant 2001). Such mechanical methods are generally more advisable than the use of anticoagulants due to the increased risk of bleeding in patients with multiple fractures and injuries (Watanabe & Sant 2001). These mechanical strategies have demonstrated positive results in the prophylaxis of DVT in patients requiring neurosurgery (Turpie et al. 1989). There is some evidence that the effectiveness of these mechanical devices in the prevention of DVT could also be increased in combination with carefully selected low-molecular weight anticoagulants that carry low bleeding risks.

Q. What is the evidence for compression stockings/pneumatic compression devices in the prophylaxis of deep venous thrombosis post ABI?

Answer

- There is Level 1b evidence that low-molecular weight heparin combined with compression stockings is more effective than compression stockings alone for the prevention of venous thromboembolism following elective neurosurgery, and that the use of low-molecular weight heparin in this setting does not cause excessive bleeding.

In a RCT conducted by Agnelli et al. (1998) patients due to undergo elective neurosurgery within 24 hours were placed on LMWH or a placebo, and were also fitted with combination compression stockings. DVTs were more common in the placebo group than the treatment group ($p<0.004$). The combination of both the compression stockings and LMWH appeared to be more beneficial than the compression stockings alone (Agnelli et al. 1998). However, when intermittent pneumatic compression devices were compared to prophylactic LMWH for the prevention of VTE, no significant differences in the development of PEs or DVTs were found between groups (Kurtoglu et al. 2004).

Deep Venous Thrombosis Recommendations (ABIKUS Guidelines; Bayley et al. 2007)

G77 (p. 28)
Deep venous thrombosis are common and potentially serious complications of TBI that can be circumvented by the use of low-molecular weight unfractionated and/or compression stockings that can be used to prevent deep venous thrombosis/pulmonary embolism post ABI. (ABIKUS B)

G78 (p. 28)
Prophylactic unfractionated heparin given early does not lead to increased intracranial bleeding in severe ABI patients. (ABIKUS B).

Reference List

Agnelli, G., Piovella, F., Buoncristiani, P., Severi, P., Pini, M., D'Angelo, A., . . . Brambilla, G. (1998). Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med, 339*(2), 80-85.

Akman, M. N., Cetin, N., Bayramoglu, M., Isiklar, I., & Kilinc, S. (2004). Value of the D-dimer test in diagnosing deep vein thrombosis in rehabilitation inpatients. *Arch Phys Med Rehabil, 85*(7), 1091-1094.

Antiplatelet Trialists' Collaboration. (1994). Collaborative overview of randomised trials of antiplatelet therapy - III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ, 308*(6923), 235-246.

Banovac, K., & Gonzalez, F. (1997). Evaluation and management of heterotopic ossification in patients with spinal cord injury. *Spinal Cord, 35*(3), 158-162.

Bayley, M., Teasell, R., Marshall, S., Cullen, N., Colantonio, A., Kua, A. (2007). ABIKUS Evidence Based Recommendations for Rehabilitation of Moderate to Severe Acquired Brain Injury. Toronto, Ontario, Canada: Ontario Neurotrauma Foundation.

Bidner, S. M., Rubins, I. M., Desjardins, J. V., Zukor, D. J., & Goltzman, D. (1990). Evidence for a humoral mechanism for enhanced osteogenesis after head injury. *J Bone Joint Surg Am, 72*(8), 1144-1149.

Brooker, A. F., Bowerman, J. W., Robinson, R. A., & Riley, L. H., Jr. (1973). Ectopic ossification following total hip replacement. Incidence and a method of classification. *J Bone Joint Surg Am, 55*(8), 1629-1632.

Browse, N. L. (1974). Current thoughts on venous thromboembolism. *Surg Clin North Am, 54*(1), 229-238.

Buschbacher, R. (1992). Heterotopic ossification: a review. *Clin Rev Phys Med Rehabil, 4*, 199-213.

Carlile, M., Nicewander, D., Yablon, S. A., Brown, A., Brunner, R., Burke, D., . . . Diaz-Arrastia, R. (2010). Prophylaxis for venous thromboembolism during rehabilitation for traumatic brain injury: A multicenter observational study. *J Trauma, 68*(4), 916-923.

Carlile, M. C., Yablon, S. A., Mysiw, W. J., Frol, A. B., Lo, D., & Diaz-Arrastia, R. (2006). Deep venous thrombosis management following traumatic brain injury: a practice survey of the traumatic brain injury model systems. *J Head Trauma Rehabil, 21*(6), 483-490.

Chantraine, A., & Minaire, P. (1981). Para-osteo-arthropathies. A new theory and mode of treatment. *Scand J Rehabil Med, 13*(1), 31-37.

Cifu, D. X., Kaelin, D. L., & Wall, B. E. (1996). Deep venous thrombosis: Incidence on admission to a brain injury rehabilitation program. *Arch Phys Med Rehabil, 77*(11), 1182-1185.

Cipriano, C. A., Pill, S. G., & Keenan, M. A. (2009). Heterotopic ossification following traumatic brain injury and spinal cord injury. *J Am Acad Orthop Surg, 17*(11), 689-697.

Citta-Pietrolungo, T. J., Alexander, M. A., & Steg, N. L. (1992). Early detection of heterotopic ossification in young patients with traumatic brain injury. *Arch Phys Med Rehabil, 73*(3), 258-262.

Corrigan, T. P., Fossard, D. P., Spindler, J., Armstrong, P., Strachan, C. J., Johnston, K. W., & Kakkar, V. V. (1974). Phlebography in the management of pulmonary embolism. *Br J Surg, 61*(6), 484-488.

Crawford, C. M., Varghese, G., Mani, M. M., & Neff, J. R. (1986). Heterotopic ossification: Are range of motion exercises contraindicated? *J Burn Care Rehabil, 7*(4), 323-327.

Davidson, J. E., Willms, D. C., & Hoffman, M. S. (1993). Effect of intermittent pneumatic leg compression on intracranial pressure in brain-injured patients. *Crit Care Med, 21*(2), 224-227.

Decousus, H., Leizorovicz, A., Parent, F., Page, Y., Tardy, B., Girard, P., Simonneau, G. (1998). A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med, 338*(7), 409-415.

Denson, K., Morgan, D., Cunningham, R., Nigliazzo, A., Brackett, D., Lane, M., . . . Albrecht, R. (2007). Incidence of venous thromboembolism in patients with traumatic brain injury. *Am J Surg, 193*(3), 380-383.

Dizdar, D., Tiftik, T., Kara, M., Tunc, H., Ersoz, M., & Akkus, S. (2013). Risk factors for developing heterotopic ossification in patients with traumatic brain injury. *Brain Inj, 27*(7-8), 807-811.

Ellerin, B. E., Helfet, D., Parikh, S., Hotchkiss, R. N., Levin, N., Nisce, L., . . . Moni, J. (1999). Current therapy in the management of heterotopic ossification of the elbow: A review with case studies. *Am J Phys Med Rehabil, 78*(3), 259-271.

Elliott, B., Patel, P., Matharu, M. S., Amos, R., Machin, S., Liu, C., & Greenwood, R. (2006). Prophylaxis of venous thromboembolism during early inpatient rehabilitation after acquired brain injury: How guidelines change management. *Disabil Rehabil, 28*(5), 333-337.

Evans, E. B. (1991). Heterotopic bone formation in thermal burns. *Clin Orthop Relat Res,* 263, 94-101.

Farooqui, A., Hiser, B., Barnes, S. L., & Litofsky, N. S. (2013). Safety and efficacy of early thromboembolism chemoprophylaxis after intracranial hemorrhage from traumatic brain injury. *J Neurosurg, 119*(6), 1576-1582.

Fuller, D. A., Mani, U. S., & Keenan, M. A. (2013). Heterotopic ossification of the shoulder in patients with traumatic brain injury. *J Shoulder Elbow Surg, 22*(1), 52-56.

Fuller, D. A., Mark, A., & Keenan, M. A. (2005). Excision of heterotopic ossification from the knee: A functional outcome study. *Clin Orthop Relat Res, 438*, 197-203.

Garcia-Fuster, M. J., Fabia, M. J., Furio, E., Pichler, G., Redon, J., Forner, M. J., & Martinez, F. (2014). Should we look for silent pulmonary embolism in patients with deep venous thrombosis? *BMC Cardiovasc Disord, 14*, 178.

Garland, D. E. (1991). A clinical perspective on common forms of acquired heterotopic ossification. *Clin Orthop Relat Res,* 263, 13-29.

Garland, D. E., Blum, C. E., & Waters, R. L. (1980). Periarticular heterotopic ossification in head-injured adults. Incidence and location. *J Bone Joint Surg Am, 62*(7), 1143-1146.

Garland, D. E., Razza, B. E., & Waters, R. L. (1982). Forceful joint manipulation in head-injured adults with heterotopic ossification. *Clin Orthop Relat Res, 169*, 133-138.

Garland, D. E., & Varpetian, A. (2003). Heterotopic Ossification in Traumatic Brain Injury. In M. J. Ashley (Ed.), *Traumatic Brain Injury: Rehabilitation, Treatment, and Case Management* (pp. 119-134). Boca Raton, FL: CRC Press.

Geerts, W. H., Code, K. I., Jay, R. M., Chen, E., & Szalai, J. P. (1994). A prospective study of venous thromboembolism after major trauma. *N Engl J Med, 331*(24), 1601-1606.

Geerts, W. H., Jay, R. M., Code, K. I., Chen, E., Szalai, J. P., Saibil, E. A., & Hamilton, P. A. (1996). A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med, 335*(10), 701-707.

Gersin, K., Grindlinger, G. A., Lee, V., Dennis, R. C., Wedel, S. K., & Cachecho, R. (1994). The efficacy of sequential compression devices in multiple trauma patients with severe head injury. *J Trauma, 37*(2), 205-208.

Gill, P., & Nahum, A. (2000). Improving detection of venous thromboembolism. New technology holds promise for early, precise diagnosis. *Postgrad Med, 108*(4), 24-26, 29-32, 38-40.

Green, D., Lee, M. Y., Ito, V. Y., Cohn, T., Press, J., Filbrandt, P. R., . . . Meyer, P. R., Jr. (1988). Fixed- vs adjusted-dose heparin in the prophylaxis of thromboembolism in spinal cord injury. *JAMA, 260*(9), 1255-1258.

Greenfield, L. J., & Michna, B. A. (1988). Twelve-year clinical experience with the Greenfield vena caval filter. *Surgery, 104*(4), 706-712.

Haddad, S. H., & Arabi, Y. M. (2012). Critical care management of severe traumatic brain injury in adults. *Scand J Trauma Resusc Emerg Med, 20*, 12.

Hirsh, J., Dalen, J. E., Deykin, D., Poller, L., & Bussey, H. (1992). Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest, 108*(4 Suppl), 231s-246s.

Hosalkar, H., Pandya, N. K., Baldwin, K., & Keenan, M. A. (2013). Neuro-Orthopedics. In N. D. Zasler, D. I. Katz & R. D. Zafonte (Eds.), *Brain Injury Medicine* (pp. 850-872). New York, NY: Demos Medical Publishing.

Hull, R., & Hirsh, J. (1983). Long-term anticoagulant therapy in patients with venous thrombosis. *Arch Intern Med, 143*(11), 2061-2063.

Hurvitz, E. A., Mandac, B. R., Davidoff, G., Johnson, J. H., & Nelson, V. S. (1992). Risk factors for heterotopic ossification in children and adolescents with severe traumatic brain injury. *Arch Phys Med Rehabil, 73*(5), 459-462.

Hyers, T. M., Hull, R. D., & Weg, J. G. (1992). Antithrombotic therapy for venous thromboembolic disease. *Chest, 108*(4 Suppl), 335s-351s.

Ippolito, E., Formisano, R., Caterini, R., Farsetti, P., & Penta, F. (1999a). Operative treatment of heterotopic hip ossification in patients with coma after brain injury. *Clin Orthop Relat Res*, *365*, 130-138.

Ippolito, E., Formisano, R., Caterini, R., Farsetti, P., & Penta, F. (1999b). Resection of elbow ossification and continuous passive motion in postcomatose patients. *J Hand Surg Am, 24*(3), 546-553.

Ippolito, E., Formisano, R., Farsetti, P., Caterini, R., & Penta, F. (1999). Excision for the treatment of periarticular ossification of the knee in patients who have a traumatic brain injury. *J Bone Joint Surg Am, 81*(6), 783-789.

Ivanhoe, C. B., Durand-Sanchez, A., & Spier, E. T. (2012). Acute Rehabilitation. In N. D. Zasler, D. I. Katz, & R. D. Zafonte (Eds.), *Brain Injury Medicine* (pp. 385-405). New York, NY: Demos Medical Publishing.

Jensen, L. L., Halar, E., Little, J. W., & Brooke, M. M. (1987). Neurogenic heterotopic ossification. *Am J Phys Med, 66*(6), 351-363.

Katsouda, E., Mystakidou, K., Rapti, A., Argentos, S., Kelekis, N. L., Mastorakou, R., . . . Kelekis, D. A. (2005). Evaluation of spiral computed tomography versus ventiliation/perfusion scanning in patients clinically suspected of pulmonary embolism. *In Vivo*, *19*(5), 873-878.

Kearon, C., Ginsberg, J. S., & Hirsh, J. (1998). The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med, 129*(12), 1044-1049.

Keret, D., Harcke, H. T., Mendez, A. A., & Bowen, J. R. (1990). Heterotopic ossification in central nervous system-injured patients following closed nailing of femoral fractures. *Clin Orthop Relat Res,* (256), 254-259.

Kim, J., Gearhart, M. M., Zurick, A., Zuccarello, M., James, L., & Luchette, F. A. (2002). Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. *J Trauma, 53*(1), 38-43.

Kjaersgaard-Andersen, P., & Schmidt, S. A. (1986). Indomethacin for prevention of ectopic ossification after hip arthroplasty. *Acta Orthop Scand, 57*(1), 12-14.

Koehler, D. M., Shipman, J., Davidson, M. A., & Guillamondegui, O. (2011). Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. *J Trauma, 70*(2), 324-329.

Kolessar, D. J., Katz, S. D., & Keenan, M. A. (1996). Functional Outcome following surgical resection of heterotopic ossification in patients with brain injury. *J Head Trauma Rehabil, 11*(4), 78-87.

Kurtoglu, M., Yanar, H., Bilsel, Y., Guloglu, R., Kizilirmak, S., Buyukkurt, D., & Granit, V. (2004). Venous thromboembolism prophylaxis after head and spinal trauma: Intermittent pneumatic compression devices versus low molecular weight heparin. *World J Surg, 28*(8), 807-811.

Kwiatt, M. E., Patel, M. S., Ross, S. E., Lachant, M. T., MacNew, H. G., Ochsner, M. G., . . . Haan, J. M. (2012). Is low-molecular-weight heparin safe for venous thromboembolism prophylaxis in patients with traumatic brain injury? A Western Trauma Association multicenter study. *J Trauma Acute Care Surg, 73*(3), 625-628.

Landefeld, C. S., & Goldman, L. (1989). Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med, 87*(2), 144-152.

Lazarus, M. D., Guttmann, D., Rich, C. E., & Keenan, M. A. E. (1999). Heterotopic ossification resection about the elbow. *NeuroRehabilitation, 12*(2), 145-153.

Lee, E. K., Namdari, S., Hosalkar, H. S., Keenan, M. A., & Baldwin, K. D. (2013). Clinical results of the excision of heterotopic bone around the elbow: a systematic review. *J Shoulder Elbow Surg, 22*(5), 716-722.

Linan, E., O'Dell, M. W., & Pierce, J. M. (2001). Continuous passive motion in the management of heterotopic ossification in a brain injured patient. *Am J Phys Med Rehabil, 80*(8), 614-617.

Macatangay, C., Todd, S. R., & Tyroch, A. H. (2008). Thromboembolic prophylaxis with intermittent pneumatic compression devices in trauma patients: a false sense of security? *J Trauma Nurs, 15*(1), 12-15.

Melamed, E., Robinson, D., Halperin, N., Wallach, N., Keren, O., & Groswasser, Z. (2002). Brain injury-related heterotopic bone formation: treatment strategy and results. *Am J Phys Med Rehabil, 81*(9), 670-674.

Moore, T. J. (1993). Functional outcome following surgical excision of heterotopic ossification in patients with traumatic brain injury. *J Orthop Trauma, 7*(1), 11-14.

Moreta, J., & de los Mozos, J. L. M. (2014). Heterotopic Ossification after Traumatic Brain Injury. In F. Sadaka & T. Quinn (Eds.), *Traumatic Brain Injury* (pp. 331-349). Retrieved from http://www.intechopen.com/books/traumatic-brain-injury

Nadler, S. F., Malanga, G. A., & Zimmerman, J. R. (1993). Continuous passive motion in the rehabilitation setting. A retrospective study. *Am J Phys Med Rehabil, 72*(3), 162-165.

Norwood, S. H., Berne, J. D., Rowe, S. A., Villarreal, D. H., & Ledlie, J. T. (2008). Early venous thromboembolism prophylaxis with enoxaparin in patients with blunt traumatic brain injury. *J Trauma, 65*(5), 1021-1026.

Norwood, S. H., McAuley, C. E., Berne, J. D., Vallina, V. L., Kerns, D. B., Grahm, T. W., . . . McLarty, J. W. (2002). Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. *Arch Surg, 137*(6), 696-702.

Palmowski, K., Oltmanns, U., Kreuter, M., Mottaghy, F. M., Palmowski, M., & Behrendt, F. F. (2014). Diagnosis of pulmonary embolism: conventional ventilation/perfusion SPECT is superior to the combination of perfusion SPECT and nonenhanced CT. *Respiration, 88*(4), 291-297.

Pape, H. C., Lehmann, U., van Griensven, M., Gansslen, A., von Glinski, S., & Krettek, C. (2001). Heterotopic ossifications in patients after severe blunt trauma with and without head trauma: incidence and patterns of distribution. *J Orthop Trauma, 15*(4), 229-237.

Pape, H. C., Marsh, S., Morley, J. R., Krettek, C., & Giannoudis, P. V. (2004). Current concepts in the development of heterotopic ossification. *J Bone Joint Surg Br, 86*(6), 783-787.

Phelan, H. A., Eastman, A. L., Madden, C. J., Aldy, K., Berne, J. D., Norwood, S. H., . . . Minei, J. P. (2012). TBI risk stratification at presentation: a prospective study of the incidence and timing of

radiographic worsening in the Parkland Protocol. *J Trauma Acute Care Surg, 73*(2 Suppl 1), S122-127.

PIOPED Investigators. (1990). Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA, 263*(20), 2753-2759.

Puzas, J. E., Evarts, C. M., & Brand, J. S. (1987). The stimulus for bone formation. *Hip,* 25-38.

Raimondi, P., Bongard, O., De Moerloose, P., Reber, G., Waldvogel, F., & Bounameaux, H. (1993). D-Dimer plasma concentration in various clinical conditions: Implication for the use of this test in the diagnostic approach of venous thromboembolism. *Thromb Res, 69*(1), 125-130.

Raslan, A. M., Fields, J. D., & Bhardwaj, A. (2010). Prophylaxis for venous thrombo-embolism in neurocritical care: a critical appraisal. *Neurocrit Care, 12*(2), 297-309.

Reiff, D. A., Haricharan, R. N., Bullington, N. M., Griffin, R. L., McGwin, G., Jr., & Rue, L. W., 3rd. (2009). Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. *J Trauma, 66*(5), 1436-1440.

Righini, M., Le Gal, G., Aujesky, D., Roy, P. M., Sanchez, O., Verschuren, F., . . . Perrier, A. (2008). Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet*, *371*(9621), 1343-1352.

Ritter, M. A., & Sieber, J. M. (1985). Prophylactic indomethacin for the prevention of heterotopic bone formation following total hip arthroplasty. *Clin Orthop Relat Res,* (196), 217-225.

Rogers, R. C. (1988). Heterotopic calcification in severe head injury: a preventive programme. *Brain Inj, 2*(2), 169-173.

Salottolo, K., Offner, P., Levy, A. S., Mains, C. W., Slone, D. S., & Bar-Or, D. (2011). Interrupted pharmocologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma, 70*(1), 19-24.

Salter, R. B. (1996). History of rest and motion and the scientific basis for early continuous passive motion. *Hand Clin, 12*(1), 1-11.

Sarafis, K. A., Karatzas, G. D., & Yotis, C. L. (1999). Ankylosed hips caused by heterotopic ossification after traumatic brain injury: a difficult problem. *J Trauma, 46*(1), 104-109.

Sazbon, L., Najenson, T., Tartakovsky, M., Becker, E., & Grosswasser, Z. (1981). Widespread periarticular new-bone formation in long-term comatose patients. *J Bone Joint Surg Br, 63-b*(1), 120-125.

Scales, D. C., Riva-Cambrin, J., Wells, D., Athaide, V., Granton, J. T., & Detsky, A. S. (2010). Prophylactic anticoagulation to prevent venous thromboembolism in traumatic intracranial hemorrhage: a decision analysis. *Crit Care, 14*(2), R72.

Scudday, T., Brasel, K., Webb, T., Codner, P., Somberg, L., Weigelt, J., . . . Peppard, W. (2011). Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. *J Am Coll Surg, 213*(1), 148-153.

Spielman, G., Gennarelli, T. A., & Rogers, C. R. (1983). Disodium etidronate: its role in preventing heterotopic ossification in severe head injury. *Arch Phys Med Rehabil, 64*(11), 539-542.

Stover, S. L., Niemann, K. M., & Tulloss, J. R. (1991). Experience with surgical resection of heterotopic bone in spinal cord injury patients. *Clin Orthop Relat Res*, *263*, 71-77.

Tapson, V. F., Carroll, B. A., Davidson, B. L., Elliott, C. G., Fedullo, P. F., Hales, C. A., . . . Taylor Thompson, B. (1999). The diagnostic approach to acute venous thromboembolism. Clinical practice guideline. American Thoracic Society. *Am J Respir Crit Care Med, 160*(3), 1043-1066.

Trentz, O. A., Handschin, A. E., Bestmann, L., Hoerstrup, S. P., Trentz, O. L., & Platz, A. (2005). Influence of brain injury on early posttraumatic bone metabolism. *Crit Care Med, 33*(2), 399-406.

Turpie, A. G. G., Hirsh, J., Gent, M., Julian, D., & Johnson, J. (1989). Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression

stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med, 149*(3), 679-681.

van Kampen, P. J., Martina, J. D., Vos, P. E., Hoedemaekers, C. W., & Hendricks, H. T. (2011). Potential risk factors for developing heterotopic ossification in patients with severe traumatic brain injury. *J Head Trauma Rehabil, 26*(5), 384-391.

van Susante, J. L., Buma, P., Kirn, H. K., & Salter, R. B. (1996). Traumatic heterotopic bone formation in the quadriceps muscle. No progression by continuous passive motion in rabbits. *Acta Orthop Scand, 67*(5), 450-454.

Vanden Bossche, L., & Vanderstraeten, G. (2005). Heterotopic ossification: a review. *J Rehabil Med, 37*(3), 129-136.

Varghese, G. (1992). Traumatic brain injury: heterotopic ossification. *Phys Med Rehabil Clin North Am, 3*, 407-415.

Vergouwen, M. D., Roos, Y. B., & Kamphuisen, P. W. (2008). Venous thromboembolism prophylaxis and treatment in patients with acute stroke and traumatic brain injury. *Curr Opin Crit Care, 14*(2), 149-155.

Watanabe, T., & Sant, M. O. (2001). Common medical complications of traumatic brain injury. *Arch Phys Med Rehabil, 15*, 283-299.

Williams, J. T., Southerland, S. S., Souza, J., Calcutt, A. F., & Cartledge, R. G. (1999). Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg, 65*(1), 22-26.

Worku, B., Gulkarov, I., Girardi, L. N., & Salemi, A. (2014). Pulmonary Embolectomy in the Treatment of Submassive and Massive Pulmonary Embolism. *Cardiology, 129*(2), 106-110.

Zierler, B. K. (2004). Ultrasonography and diagnosis of venous thromboembolism. *Circulation, 109*(12 Suppl 1), I9-14.