11. Heterotopic Ossification and Venous Thromboembolism

Robert Teasell MD FRCPC, Jo-Anne Aubut BA, Shawn Marshall MSc MD FRCPC, Nora Cullen MSc MD FRCPC
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Key Points

**Pathophysiology of heterotopic ossification is not known.**

**Heterotopic ossification is common and most often involves hips, shoulders and elbows.**

**Forceful joint manipulation increases range of motion in heterotopic ossification.**

**Continuous passive range of motion devices may increase range of motion.**

**Etridoneate prevents the development of heterotopic ossification in brain injuries.**

**Surgical excision of heterotopic ossification improves outcomes.**

**The administration of chemical prophylaxis within the first 72 hours post ABI has been shown to be effective in reducing the risk of developing DVTs or PEs without increasing the risk of intracranial bleeding; however, more research is needed.**

**Fondaparinux has been shown to be effective in the prevention of DVTs post TBI.**

**Enoxaparin is effective for the prevention of VT after elective neurosurgery and has not been found to cause excessive bleeding.**

**Low-molecular-weight heparin is more effective than low-dose heparin in preventing venous thromboembolism after severe trauma.**

**Low-molecular weight heparin is as effective and safe as unfractionated heparin for the prevention of pulmonary embolism.**

**A combination of low-dose heparin (LDH) and sequential compression devices (SCDs) demonstrated no advantage over SCD alone in reducing DVT rates in critically ill patients.**

**SCDs do not reduce the risk of developing DVTs or PEs post ABI. Intermittent compression devices do not aggravate intracranial hemodynamics in severe ABI patients.**
11. Heterotopic Ossification and Venous Thromboembolism Post ABI

11 - Heterotopic Ossification

Heterotopic ossification (HO) is a process where new bone forms within tissues where bone formation does not usually occur (Watanabe and Sant 2001). In traumatic brain injury (TBI) patients, the areas which are most commonly involved are the soft tissues around the hip, elbow, shoulder and knee (Garland 1991; van Kampen et al., 2011). The incidence of HO in TBI patients has been reported as ranging from 11% to 77% but the disease only reaches clinical significance in 11-35% of this group (Garland et al., 1980; Sazbon et al., 1981; Rogers 1988). Skeletal trauma, spasticity, immobilization, injury severity and prolonged coma greater than 2 weeks are considered to be at highest risk (Gennarelli 1988; Roberts and Pankratz 1979; van Kampen et al., 2011).

HO is often quite painful, at times limiting a patient’s ability to participate in rehabilitation. In addition, it can cause restricted joint range of motion and thereby further add to their disability by restricting mobility or functional abilities. HO therefore can potentially impede progress of patients towards their desired rehabilitation goals.

11.1 Formation of Heterotopic Ossification Post-Head Injury

11.1.1 Pathophysiology of Heterotopic Ossification Post-Head Injury
The pathophysiology of HO is not well understood. HO forms through a typical process beginning with the formation of osteoid 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, these patients develop peri-articular and intramuscular bone formation and experience restricted range of motion, pain and ankylosis (Garland et al., 1980; Banovac and Gonzalez 1997). 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 number of osteoclasts found in normal bone (Puzas et al. 1987). It is believed that there is likely a neurogenic factor contributing to HO, although this mechanism is not yet understood (Pape et al., 2001; Pape et al., 2004; Hurvitz et al., 1992).

11.1.2 Mesenchymal Stem Cells
Pape et al. (2004) noted that mesenchymal stem cells can generate cartilage, bone, muscle, tendons, ligaments or fat (Williams et al., 1999) and are thought to play a pivotal role in the development of HO.
11.1.3 Stimulating Factors Related to Head Injury

It has been noted that circulating factors promoting heterotopic ossification may be present in head injured patients (Pape et al., 2004). In one animal study, the serum from patients with head injuries has been shown to promote mitogenesis and cell division in a rat osteoblast cell culture model (Bidner et al., 1990). Trentz et al. (Trentz et al., 2005) have noted that many studies have shown enhanced osteogenesis in patients sustaining traumatic brain injury (TBI). Accelerated fracture healing and heterotopic ossifications are well-known phenomena in these patients (Bidner et al., 1990; Keret et al., 1990). Heterotopic ossification also has been reported after a wide range of central nervous system lesions, such as spinal cord injury, traumatic brain injury, cerebrovascular accident, encephalomyelitis, anoxic encephalopathies, poliomyelitis, tabes dorsalis, brain neoplasm, multiple sclerosis, syringomyelocele, and arachnoiditis (Pape et al., 2004; Jensen et al., 1987).

Conclusions

The pathophysiology of heterotopic ossification is not fully established.

Pathophysiology of heterotopic ossification is not known.

11.2 Clinical Presentation of Heterotopic Ossification

11.2.1 Location of Lesion
The most commonly affected joint is the hip, then the shoulders, elbows and rarely the knee (Garland et al., 1980). Sarafis et al. (1999) have noted that the incidence of heterotopic ossification in TBI patients is 10 to 20% (Garland 1988; Garland 1991) with the hip being the most frequent site of ossification. Hip involvement results in 18 to 37% restriction of range of motion (Sarafis et al., 1999). Total ankylosis of the joint occurs in 5-16% of affected hips (Stover et al., 1991).

Sarafis et al. (1999) have noted that the distribution of HO around the elbow occurs most commonly either anteriorly in the flexor muscles or posteriorly in the extensors. Of the joints affected by heterotopic ossification after head injury, ankylosis is most likely to occur in the elbow and it usually occurs posteriorly (Garland et al., 1980).

Sarafis et al. (1999) have noted that the knee is a rare site of heterotopic ossification following head injury. The most common site in the knee is the inferomedial aspect of the distal femur.

11.2.2 Clinical Features
Pape and colleagues (2004) have noted that clinical examination may reveal a swollen, warm, painful joint which is often associated with a decreased range of motion. Watanabe and Sant (2001) have reported that the formation of HO generally precedes symptom onset with the
earliest sign often being decreased range of motion in the involved joint. Other findings then include swelling, warmth, erythema, pain, palpation of a peri-articular mass and fever (Varghese, 1992). It is therefore difficult to differentiate heterotopic ossification from infection because of the association with fever (Garland et al., 1980; Garland1991; Citta-Pietrolungo et al., 1992). The clinical picture may be confused with deep venous thrombosis (DVT), a local infection, local trauma or fracture (Buschbacher 1992; Jensen et al., 1987).

Watanabe and Sant (2001) have noted that HO is generally initiated within 2-3 weeks of the onset of the injury; however, Szabolcs et al. (1981) have reported onset 1 to 7 months following the TBI. During the initial presentation, plain radiographs may be negative and will usually remain normal until ossification begins 4-6 weeks post injury. Serum levels of alkaline phosphatase and the erythrocyte sedimentation rate may become elevated early on. The triple phase technicium-99 bone scan with increased uptake during the first and second phases remains the diagnostic gold standard, becoming positive at about the same time as clinical features occur.

Conclusions

10 – 20% of TBI patients develop heterotopic ossification. The hips, shoulders and elbows are most commonly affected. Clinical features include warm, swollen painful joint with some restriction of ROM.

Heterotopic ossification is common and most often involves hips, shoulders and elbows.

11.3 Treatment of HO Post-Head Injury
Watanabe and Sant (2001) have noted that prophylactic treatment options include range of motion exercises, nonsteroidal anti-inflammatory medications (NSAIDs), low-dose radiation, warfarin, and etidronate disodium (EHDP).

11.3.1 Physiotherapy and Range of Motion Exercises
Range of motion exercises has been somewhat controversial with some earlier reports suggesting that physical therapy might actually contribute to HO (Chantraine and Minaire 1981; Crawford et al., 1986). More recently there has been a trend towards utilizing physical therapy with range of motion exercises and even manipulation under anaesthesia of the involved joints (Garland 1991; Garland et al., 1982) to help prevent ankylosis. Pape et al. (2004) have noted that for HO, careful and judicious use of physiotherapy involving assisted range of motion exercises and gentle stretching has been shown to be of benefit (Ellerin et al., 1999). However, Pape et al. (2004) caution that care should be taken not to move the joint beyond its pain-free range of movement as this can exacerbate the condition (Evans, 1991).
Table 11.1 Physiotherapy and Range of Motion Exercises as Treatment for HO

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<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
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<tr>
<td>Garland et al., (1982) USA Case series</td>
<td>N=16 Retrospective study of patients who underwent manipulation under general anesthesia. Patients ranged in age from 17 – 35 years (mean = 24). All injuries were the result of high-energy accidents. Joints were manipulated an average of 3.6 months after head injury. Follow-up from time of joint manipulation averaged 15 months.</td>
<td>Gains in range of motion were made in 23/28 (82%) of the number treated with 18/28 (64%) joints maintaining or gaining further motion with rehabilitation.</td>
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</table>

Discussion

Garland et al. (1982) conducted a review of TBI patients who underwent forceful manipulation under anaesthesia and reported that it was useful in maintaining and increasing range of motion in TBI patients. Garland et al. (1982) reported that in their study, gains in motion were made in 23/28 (82%) of the joints treated with manipulation under anesthesia and 18/28 (64%) joints maintained or gained further motion with rehabilitation. Garland et al. (1982) suggested that “forceful manipulation of joints with pre-existing heterotopic ossification has a role in maintaining a useful arc of joint motion and in prevention of bone ankylosis. Moreover, the results of this study suggest that manipulation does not appear to speed up or worsen the process of ossification.

It has also been noted that because these patients frequently suffer from spasticity, intolerance to pain and voluntary muscle guarding, anaesthesia is needed to help differentiate between spasticity and ankylosis and allow sufficient muscle relaxation to perform the forceful manipulation (Garland and Varpetian 2003).

Conclusions

There is Level 4 evidence that forceful manipulation under general anesthesia increases range of motion in patients with heterotopic ossification following brain injury.

Forceful joint manipulation increases range of motion in heterotopic ossification.

11.3.2 Continuous Passive Motion

Continuous passive motion devices have shown promising results in maintaining range of motion following total knee replacement (Salter, 1996; Nadler et al., 1993). According to Linan et al. (2001) there is little research evidence that HO is worsened by passive range of motion. Animal data also shows that continuous passive motion does not increase the progression of HO (van Susante et al., 1996).
Individual Studies

Table 11.2 Continuous Passive Motion Devices in the Treatment of HO

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<th>Author/Year/Country/Study design</th>
<th>Methods</th>
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<tr>
<td>Linan et al., (2001) USA Case Study No score</td>
<td>N=1 Single case study of a 27 year old male admitted to inpatient rehabilitation with bilateral knee heterotopic ossification 6 weeks after severe TBI (GCS = 3). The patient was treated with a continuous passive motion device during for 4 weeks.</td>
<td>At discharge from inpatient rehabilitation 90 days after injury, the range of motion of the right knee increased to 84 º and the left knee to 75 º compared with 10-25 º and 10-20 º respectively before treatment. Six months after the injury, the patient was independent for ambulation with a straight cane and in activities of daily living. 2 years after the injury, significant improvements in flexion of bilateral knees were still observed. However, the lack of end extension of bilateral knees remained almost unchanged likely caused by the presence of HO blocking the joints.</td>
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</table>

Discussion
Linan et al. (2001) reported on a case admitted to an inpatient rehabilitation unit 6 weeks post TBI who presented with bilateral knee HO. In addition to conventional physical therapy the authors applied a continuous passive motion device during 4 weeks increasing the range of motion of the knees. Moreover, the findings of Linan et al. (2001) support the notion that continuous passive range of motion does not worsen HO, and thus additional studies should investigate its effects on maintaining or improving range of motion in brain injury patients who develop HO.

Conclusions
There is Level 5 (limited) evidence that continuous passive motion reduces the development of heterotopic ossification in severe head injury patients.

Continuous passive range of motion devices may increase range of motion

11.3.3 Nonsteroidal Anti-Inflammatory Medications
The evidence for NSAIDs being used in prophylactic treatment of HO comes mostly from the use of indomethacin or ibuprofen prophylaxis against HO in patients following total hip arthroplasty (THA) (Kjaersgaard-Anderson & Schmid, 1986; Ritter & Sieber, 1985).
Although it has been noted that these medications offer a significant benefit in prophylaxis of THA, the correlation of these findings in traumatic brain injuries is not known (Watanabe & Sant, 2001).

11.3.4 Ethylhydroxybiphosphonate (EHDP)
Watanabe and Sant (2001) have noted that biphosphonates, in particular etridonate (EHDP) in 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. In a small study Spielman et al. (1983) showed EHDP reduced the development of HO in patients with TBI. Most of the research has been on spinal cord injured patients. Finerman and Stover (1981) and Stover et al. (Stover et al., 1976) reported that EHDP resulted in a significant reduction in HO in SCI patients while Garland et al. (1983) noted that EHDP failed to prevent HO in the hips of SCI patients being treated for HO already present in other joints (Watanabe and Sant 2001). Pape et al. (2004) have noted that there has been a lack of conclusive evidence to show that etridonate arrests the development of HO (Garland 1991; Citta-Pietrolungo et al., 1992; Shehab et al., 2002; Pelissier et al., 2002). Etridonate may potentially delay fracture healing, as long-term use has been associated with osteomalacia. EHDP can lead to nausea, diarrhea and joint pain, which can be improved by dividing the daily dose (Spielman et al., 1983).

Individual Studies

Table 11.3 Prophylactic Treatment of HO with EHDP

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<th>Author/Year/Country/Study design</th>
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<td>Spielman et al., (1983) USA Non-RCT</td>
<td>N=20 2 group non-RCT comparative study to assess the prophylactic effect of EHDP in decreasing the incidence of HO in severe head injury patients (GCS ≤ 8). 10 patients were treated with EHDP while 10 patients received no treatment. Treatment began within 2 – 7 days after injury. EHDP treatment lasted 6 months, at a rate of 20 mg/kg/day for the first 3 months and 10 mg/kg/day for the last 3 months.</td>
<td>There were no statistically significant group differences in terms of injury severity (GCS), age distribution, sex ratios, the presence of fractures, length of coma, type of head injury and limb spasticity. The EHDP treated group showed a significantly lower incidence of HO compared with controls (2 patients in the EHDP treated group developed HO compared with 7 of the control patients, p &lt; 0.025).</td>
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Discussion
One prospective controlled trial examined the effectiveness of EHDP treatment for the management of HO following brain injury (Spielman et al. 1983). Treatment began two to seven days post injury and lasted for a period of six months. The group of patients treated with EHDP showed a significantly lower incidence of HO when compared with the control group. Further research assessing the benefit of EHDP for the treatment of HO following brain injury is needed.
Conclusions

There is Level 2 evidence that etridonate (EHDP) reduces the development of heterotopic ossification in severe head injury patients.

11.4 Surgical Excision

Surgical excision of the heterotopic bone has been suggested as a possible option for those in whom heterotopic ossification has generated marked functional impairment or ulcers in the skin due to deformity (Watanabe and Sant 2001). According to expert opinion, surgical treatment should be considered only after 12-18 months to ensure that the bone tissue has matured, and to reduce the likelihood of recurrence (Sazbon et al., 1981; Garland, 1991b). There are some indications that EHDP and NSAIDs may be useful in preventing HO recurrence following surgical excision (Watanabe and 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-operatively.

Individual Studies

Table 11.4 Surgical Excision of HO

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<tr>
<th>Author/Year/Country/Study design</th>
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<tr>
<td>Charnley et al., (1996) France Case Series</td>
<td>N=5 A single group intervention of head injured patients, mean age 28.4 yrs, all of whom had been in a coma for 1-4 months following a MVA. All developed HO &gt; 18 months post-injury and in all cases knee joint was one of only several joints operated upon to improve mobility. Patients underwent surgical excision of HO around the knee and postoperatively, all patients underwent early rehab to maintain function. All had ice applied locally and were given indomethacin to prevent recurrence of HO.</td>
<td>Follow-up evaluation a minimum of 12 months post-op and mean of 18 mos. There was no delayed wound healing or recurrence of HO about the knee. All patients had significant pain relief and all had improved ROM. Overall benefit meant patients could lie in bed, sit and transfer with greater ease and comfort. Three of the 5 showed marked improvements in mobility, 2 being able to walk without aids or assistance.</td>
</tr>
<tr>
<td>de Palma et al., (2002) Italy Case Series</td>
<td>N=10 ABI patients (14 elbows in total) underwent surgical resection of elbow HO 18-20 months after the onset of HO. Patients were graded according to Garland’s classification (Garland et al. 1985). Indomethacin was administered</td>
<td>Improved range of motion in the early postoperative period in all patients, but especially in those with the most severe restriction in joint movement. Improvement correlated with residual neurological damage since class I and II</td>
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<td>Author/Year/Country/Study design</td>
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<td>postoperatively (25 mg 3 times a day for 6 weeks) to prevent relapses. One month postoperatively, patients started active mobilization of the elbow joint. Elbow Range of Motion (ROM) evaluated post-treatment.</td>
<td>patients (minimal spasticity) improved more compared with the other groups and achieved satisfactory ROM, while class III (severe spasticity) patients only showed partial improvement in ROM.</td>
</tr>
<tr>
<td>Ippolito et al., (1999a) Italy Pre-Post</td>
<td>N=12 ABI patients (all from motor vehicle accidents) underwent surgical resection of hip HO (13 hips in total). Walking capacity, Hip Range of Motion (ROM), Quality of Life were assessed.</td>
<td>All patients showed satisfactory ROM following the surgery. Although radiographs revealed remnants of HO following surgery, these remnants did not interfere with ROM. At final follow up, eight hips maintained initial gains in ROM, two decreased ROM with no evidence of HO recurrence and three decreased ROM with partial or full recurrence of HO. Five patients who had a painful hip prior to operation were free of pain at follow-up. At follow-up, 10 of 12 patients able to ambulate, but five needed either hip braces or crutches. The three patients able to ambulate independently prior to surgery demonstrated a marked gait improvement.</td>
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<tr>
<td>Ippolito et al., (1999b) Italy Case Series</td>
<td>N=14 Patients with HO of the elbow after severe TBI and coma (range 16-120 days) underwent surgical resection of the HO. Immediately after the surgery, a continuous passive motion machine was applied in an attempt to prevent postoperative loss of motion and recurrence of HO. The range of motion applied by the machine was gradually increased until the joint regained the whole arc of motion achieve at time of surgery. This machine was used on the affected elbow for 6 weeks after surgery before starting a fully active rehab program. Arc of elbow range of motion was evaluated at follow up.</td>
<td>Follow up period ranged from 12-66 months. Patients were categorized into two groups. Group 1: elbows in which the ulnohumeral articulation was ankylosed in a position that ranged from 0 to 100° (11 elbows). Group 2: elbows in which a few (10 – 25°) degrees of flexion were present (5 elbows). At the end of surgery, arc of flexion attained ranged from 90-145° in group 1 and 115-140° in group 2. At final follow-up, arc of flexion (both active and passive) attained ranged from 30-135° in group 1 and 80-145° in group 2. Patients with poor neuromuscular control lost part of their postoperative ROM and partial recurrence was observed in 3 elbows. For the 11 elbows that underwent surgery &lt; 18 months after the end of coma, the average arc of flexion was 105°, whereas for the 5 elbows treated &gt; 18 months after it was 92°.</td>
</tr>
<tr>
<td>Ippolito et al., (1999c)</td>
<td>N=5 TBI patients (seven knees) underwent surgical resection of knee</td>
<td>Latest follow up evaluation performed on average 34 months (range 25-60 months)</td>
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<tr>
<td>Author/Year/Country/Study design</td>
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<tr>
<td><strong>Italy</strong>&lt;br&gt;Case Series</td>
<td>HO. Immediately after the surgery, a continuous passive motion machine was applied in an attempt to prevent postoperative loss of motion and recurrence of HO. The machine was set up to work along the maximum painless range of motion which was gradually increased until the joint regained the whole arc of motion achieved at time of operation. Patients used this machine for &gt; 1 month following operation at night and during the day between periods of active exercise. Arc of knee motion evaluated post-treatment.</td>
<td>after the operation. The arc of motions markedly improved in all of the knees (0 – 130 degrees in 3 knees, 0 – 120 degrees in 3 knees, and 10 – 120 degrees in one knee). At follow up, one knee had an arc of flexion of 0 – 90 degrees, 2 an arc of 10 – 100 degrees, one an arc of 5 – 110 degrees, 2 and arc of 0 – 120 degrees, and one an arc of 0 – 130 degrees. Ossification did not recur in any of the knees. None of the patients could walk before operation. At follow up, all patients could walk and all knees were pain free; only one patient needed to use a cane.</td>
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<tr>
<td>Lazarus et al., (1999)&lt;br&gt;USA&lt;br&gt;Pre-Post</td>
<td>N=24 Patients with TBI and concomitant elbow HO, avg. age at time of surgery = 37.4 years, time since injury to surgery = 35.4 mos, 5 patients had also suffered a fracture or fracture/dislocation of involved elbow. 23 of the resections were primary and 3 were revisions.</td>
<td>Maximum flexion increased from 80.1 degrees preoperative to 111.9 postoperative (p=.0003). Maximum extension increased from 58.9 degrees preoperative to 32.1 postoperative (p=.0005). In the 17 patients who had ankylosed elbow preoperatively, the avg. gain in ROM was 59.1 degrees and compared to a gain of 23.2 degrees in the remaining patients (p=.03). Time from injury until resection was a significant predictor of outcome, with longer times associated with worse outcomes (p=.02). Patients who had HO from TBI without associated elbow trauma had a worse outcome that those who did have local trauma in addition to their TBI (p=.01). Those patients who had continuous passive motion (CPM) after surgery had better ROM gain than those that did not have CPM (p=.04).</td>
</tr>
<tr>
<td>Melamed et al., (2002)&lt;br&gt;Israel&lt;br&gt;Pre-Post</td>
<td>N=9 ABI patients (eight hips, three knees, and one elbow) underwent surgical resection of HO. All patients received postoperative physical therapy and participated in a rehabilitation program. Functional Status, Range of Motion (ROM), subjective measures of outcomes before and at follow up were evaluated.</td>
<td>The average follow up time was 18 months (range 9-50 months). 7/8 patients graded themselves as functionally improved. Improved ROM was documented in 7/8 patients.</td>
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<tr>
<td>Fuller et al., (2005)&lt;br&gt;Pre-Post</td>
<td>N=17 ABI patients (22 knees) underwent surgical resection of HO at the knee. All</td>
<td>Significant improvement in arc of motion (mean 65º, $p&lt; 0.0001$) following HO</td>
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</table>
Author/Year/Country/Study design | Methods | Outcome
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USA Case Series | patients then participated in an inpatient rehabilitation program consisting of ROM exercises, gently passive stretching, and immediate weight bearing as tolerated. All patients were given 20mg/kg etidronate disodium once daily for 2 months as prophylaxis against HO recurrence. Passive Range of Motion (ROM) of the knee, Five-level Ambulatory scale (Keenan 1984) and sitting function scale (created by the authors of this study) were evaluated at two weeks, six weeks, and 12 weeks postoperatively. | excision. Extension and flexion significantly improved postoperatively (p<0.0002, p<0.0001 respectively). Significant improvements in ambulation and sitting ability postoperatively (both p<0.0001). There were no recurrences of HO by clinical or radiographic examination.

Moore (1993) USA Case Series | N=17 TBI patients with ankylosed joints were subjected to surgical excision of the HO (13 resections of the hip and 7 resections of the elbow). Patients also received diphosphonates (10 mg/kg a day of etidronate disodium) for a variable length of time post-operatively, usually 3 months. Preoperative functional goals were enhanced wheelchair sitting (10 patients), improvement in bed-to-wheelchair transfers (2 patients), and improvement of gait (1 patient) for those who received hip HO resection. For those who received elbow HO resection goals included improvement of activities of daily living (6 patients) and improved hygiene (1 patient). | The average follow up time was 23 months (range 11-46). The average arc of motion obtained immediately after surgery was 85º in HO resected hips (range 70-120º) and 65º for elbows (range 20-120º). 11 hip joints and 6 elbow joints maintained sufficient ROM to achieve pre-operative functional goals. 3 joints had recurrence of HO. No statistical comparisons reported.

Discussion
We identified ten studies that explored the recurrence of HO following surgical procedures for patients with TBI. Charnley et al. (1996) noted marked improvements in mobility for three of five patients following surgical procedures. Koressar et al. (1996) studied 17 TBI adult patients (24 surgical procedures) with HO formation who underwent surgical excision. Although patients showed initial improvements, HO recurred in 23.8% of the study population based on the Brooker classification. Conversely, using Stover classification, HO recurred in only one patient. Of 11 hip and 10 elbow procedures, all patients showed significant improvements. Of three knee procedures, two achieved pre-operative goals (Koressar et al. 1996). Lazarus et al. (1999) studied 24 patients with TBI and concomitant elbow HO and noted increases in maximum flexion post-operatively. It is worth noting that time from injury until resection was found to be a significant predictor of outcome, as longer times were associated with less improvement.
(Lazarus et al. 1999). de Palma et al. (2002) also reported improved range of motion following HO resection of the elbow. Moreover, these authors noted that improvements were more pronounced in patients who showed the largest restriction in joint movement before the surgical procedure. In another single case intervention study, Ippolito et al. (1999a) conducted HO surgical resection at the hip in 12 ABI patients. The authors reported that all patients recovered satisfactory range of motion post-operatively. However, at follow-up, three patients showed a decrease in range of motion with partial or full HO recurrence (Ippolito et al. 1999a). In another study by the same authors, range of motion and walking capacity also improved following surgical excision of HO at the knee in 5 TBI patients (Ippolito et al. 1999c). These authors reported similar improvements in range of motion following surgical resection of HO at the elbow (Ippolito et al. 1999b). In a recent and similar study of surgical resection of HO at the knee, Fuller et al. (2005) reported significant improvements in arc of motion, extension and flexion, ambulation, and sitting ability postoperatively in 17 ABI patients.

**Conclusions**

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

*Surgical excision of heterotopic ossification improves outcomes.*
11 - Venous Thromboembolism

Venous thromboembolism, including deep venous thrombosis and pulmonary embolism, remains a common complication in patients who have sustained an acquired brain injury (Scudday et al., 2011; Raslan et al., 2010). However, the scientific literature, specific to ABI, is quite limited on this topic even though it is quite extensive on venous thromboembolism in general.

11.5 Incidence of Venous Thromboembolism Post-Head Injury

The reported incidence of deep venous thrombosis among patients with traumatic brain injury ranges from 11% to 54% (Cifu et al., 1996; Geerts et al., 1994; Carlile et al., 2010; Denson et al., 2007). According to a recent study by Haddad & Arabi (2012), the risk of developing a DVT or PE in the absence of prophylaxis is estimated to be approximately 20% post TBI. Despite this there are no best practice guidelines or recommendations for treatment within this group (Bratton et al. 2007). As the data evaluating the effectiveness and efficacy of the available pharmacological prophylaxes are limited, decisions on when to begin treatment and what treatment to choose is often made on a case by case basis (Tang and Lobel 2009). Unless contraindicated, mechanical thromboprophylaxis is recommended in the acute phase of recovery (Haddad & Arabi, 2012). Low molecular weight heparin is also recommended again provided there are no contraindications. Experts recommend beginning pharmacological treatments as early as 48 to 72 hours post injury (Norwood et al., 2001).

Cifu et al. (1996) in a prospective, sequential case series, screened 81 traumatic brain injured and 71 atraumatic brain injured patients, admitted to a tertiary care brain injury rehabilitation center over a 12 month period of time, within 24 hours of admission for a lower extremity DVT with color flow duplex Doppler ultrasonography. All patients were admitted within 2 months of the onset of their brain injury and all the patients had received prophylactic treatment with either subcutaneous heparin anticoagulation or intermittent compression devices. The overall incidence of DVTs was 13% while individuals with traumatic brain injury have an incidence as high as 20%. Most of the DVTs were asymptomatic.

In a current study of individuals who had sustained a TBI, DVT was present in 31.6% of patients (Ekeh et al., 2010). Those diagnosed with a DVT spent approximately 18.1 days in ICU, on average 8 days longer than those without a DVT. Those who developed a DVT were found to be significantly older (>/=55 years), male, had an ISS>15, had experienced an injury to the lower extremity and had were diagnosed with a subarachnoid hemorrhage. DVTs were located for 84% in the lower extremities (below the knee) or in the femoral artery. Of those who had sustained an isolated head injury, 25.8% developed a DVT, but of those who had sustained combined with an extracranial injury 34.3% developed a DVT (Ekeh et al., 2010).
11.6 Risk Factors for DVT

Watanabe and Sant (2001) have noted that the most recognized risk factor for venous thromboembolism are venostasis, intimal damage of the vessel wall, and a hypercoagulable state (Virchow’s triad - see Diagram 1).

Patients with a severe brain injury are commonly immobilized for periods of time as a result of the fractures they experience in extremities or spine (Vergouwen et al. 2008). The incidence of DVT appears to be impacted by length of stay in the ICU and number of days a patient is on a ventilator; however, there does not appear to be a correlation between initial GCS, Injury Severity Scale scores, or the Abbreviated Injury Scale score (AIS) (Denson et al., 2007). Those at highest risk post injury are those who remain on a ventilator longer than 3 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 venous thromboembolism.

Overall there is a lack of persuasive evidence to guide decisions about when to administered 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)

11.7 Diagnostic Testing

11.7.1 Venous Ultrasound

Venous ultrasound is often used to diagnose a DVT. The sensitivity of the test is 95% in all patients with symptomatic proximal DVTs. The sensitivity falls to 73% for distal DVTs. However, distal DVTs are generally not dangerous until they extend proximally at which point they are at a much higher risk of going up to become a pulmonary embolus. Since the majority of DVTs that do extend do so within the first week, serial testing may be all that is needed if the test is normal but the patient remains symptomatic – the test is likely to become positive as the clot extends proximally.

11.7.2 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.
11.7.3 D-dimer Assay
D-dimer assay tests are a rapid, non-invasive and inexpensive test. Fibrin is the main component of thrombus formation – fibrin degradation products include d-dimers (Gill and Nahum 2000). A positive d-dimer test is highly sensitive but lacks specificity since d-dimers are found in other disease states, including cancer, congestive heart failure and inflammatory conditions (Raimondi et al., 1993). D-dimer assays have a high negative predictive value, which means that when it is negative it is unlikely that the patient has a DVT. However, it has poor positive predictive value so that when it is positive it could be something else and you don’t know if in fact a DVT accounts for the clinical picture. 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 rehabilitating patients admitted with a diagnosis of stroke, spinal cord injury, hip arthroplasty or traumatic brain injury. The specificity and positive predictive values were low, at 55.3% and 48.7%.

11.7.4 Diagnosis of DVT
A positive diagnosis of DVT can only be made if the venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. A negative diagnosis for DVT can be made 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, or 2) normal d-dimer test, or 3) normal serial testing with testing conducted one week later. In a recent survey Carlile et al. (2006) of the acute trauma centres who responded, 56% report the use of venous duplex ultrasonography to screen for DVTs post ABI. Of the rehabilitation hospitals who responded to the survey, 13% use D-dimer along with VDU for routine screening of DVTs post injury.

11.7.5 Clinical Presentation of Pulmonary Embolus
The clinical presentation of pulmonary embolus is often unreliable, being both insensitive and non-specific. Many cases are clinically silent with only 30% having the clinical features of a DVT and only 70% demonstrating a DVT on venography. Patients with a massive pulmonary embolus who suffer compromise of more than 60% of the pulmonary circulation are critically ill. Right heart failure may progress to cardiovascular collapse with hypertension, coma and death. A submassive pulmonary embolus presents with tachycardia, tachypnea and signs of pulmonary infarction with consolidation, rales, hemoptyis, pleuritic chest pain, pleural friction rub, pleural effusion and fever. In most cases there are usually only a few clinical findings and the presentation may be non-specific with the major clinical complaints of malaise and a fever.

11.7.6 Ventilation/Perfusion Scanning
Nuclear ventilation/perfusion scans are often used to diagnose a PE. A normal perfusion scan excludes a PE but is found in the minority of patients with a PE. Perfusion defects are non-specific; about a third of those with defects actually have a PE. The probability that a perfusion defect is a PE increases with the size, shape and number of defects as well as the presence of a normal ventilation scan. Mismatched perfusion defects (normal ventilation scan), which are
segmental in size or larger are “high probability” defects and are associated with approximately an 80% prevalence of PE. Three or more mismatched defects are associated with a prevalence of approximately 90%. If a patient has a positive V/Q scan and high clinical suspicion of a PE then they should be treated.

Table 11.5 Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Clinical Suspicion in PIOPED Study

<table>
<thead>
<tr>
<th>Ventilation-Perfusion Scan Results</th>
<th>Clinical Suspicion of Pulmonary Embolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>High probability</td>
<td>56%</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>16%</td>
</tr>
<tr>
<td>Low probability</td>
<td>4%</td>
</tr>
<tr>
<td>Normal/near-normal probability</td>
<td>2%</td>
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</tbody>
</table>

* Percentage of patients with pulmonary embolism; Adapted from the PIOPED Investigators (PIOPED Investigators 1990; Gill and Nahum 2000).

PIOPED demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of pulmonary embolism essentially excludes the diagnosis of pulmonary embolism (negative predictive values of 96% and 98% respectively) (Gill and Nahum 2000; PIOPED Investigators 1990). When clinical suspicion is high and the scan indicates a high probability of pulmonary embolism, the positive predictive value is 96% (Gill & Nahum, 2000; PIOPED Investigators, 1990).

11.7.7 Pulmonary Angiography

Pulmonary angiography is the definitive diagnosis for pulmonary embolism (Gill and Nahum 2000). It involves percutaneous catheterization and injection of contrast dye into a pulmonary artery branch (Gill and Nahum 2000). It is used when the V/Q scan is nondiagnostic but the clinical suspicion remains high. It is an expensive test and is associated with some significant risk of complications. Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill and Nahum 2000). It is associated with a mortality rate of up to 0.5% (Stein et al., 1992). Pulmonary angiography is most commonly used when ventilation-perfusion scanning is nondiagnostic but clinical suspicion remains high (Tapson et al., 1999). A negative pulmonary angiogram excludes clinically relevant pulmonary embolism (Gill and Nahum 2000; Tapson et al. 1999).

11.7.8 Spiral CT Scan

A spiral CT scan is a quick CT scan which can scan the entire thorax in one breath-hold. It has a sensitivity ranging from 64-93% with a specificity of 89-100% - it is most accurate when the embolism is large and less accurate when the clot is small. It actually visualizes the clot and has the added benefit of diagnosing other disease states in the differential diagnosis. It is also a less expensive test. The majority of ventilation perfusion scans have nondiagnostic results, requiring further testing (PIOPED Investigators 1990).
11.8 Treatment s for DVTs Post ABI

To date, the recommendation for treating those who sustain a DVT post ABI is the administration of medication in combination with sequential compression devices (Scudday et al., 2011; Elliott et al., 2006); however there is no agreement on when to administered these medications, how much, the type and the dose.

11.8.1 Pharmaceutical Therapies

Oral agents have been investigated for their prophylactic potential against DVT. Warfarin (coumadin), an efficient and 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 and Sant 2001). However, some experts believe that the use of warfarin is still advisable, especially for high risk patients due to its benefit in treating undetected thromboses, which are not uncommon in this group of patients and also because the therapeutic concentration for prophylaxis and treatment of thromboembolism are the same (Hirsh et al., 1992; Hyers et al., 1992; Landefeld and Goldman 1989). In a recent study, out of the 932 patients enrolled, 71% were given low-molecular weight heparin (LMWH), 23% heparin, and 1% coumadin, 3% were given both LMWH and unfractionated heparin (LDUH) (Carlile et al., 2010). The administration of these medications did not increase the risk of intracranial or systematic hemorrhaging. The most recent guidelines on DVT prophylaxis recommend using LMWH or LDUH in addition to mechanical prophylaxis when treating DVT post ABI (Reiff et al., 2009; Elliott et al., 2006). There is also evidence from a meta-analysis, that aspirin has positive effects in the reduction of both DVT and pulmonary embolism, with reductions of up to 40% and 60% respectively (Antiplatelet Trialists’ Collaboration, 1994). However, due to an attending physician’s fear of exacerbating or expanding the intracranial bleed, treating DVTs with any anticoagulant prophylaxis remains an individual physician’s choice (Carlile et al., 2006). To date no national standard of care exists for the administration of the pharmacological prophylaxis treatment of DVT post TBI (Phelan et al., 2012).

Individual Studies

Table 11.6 Unfractionated Heparin or Low Molecular Weight Heparin (LMWH) vs Placebo

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minshall et al., (2011) USA Retrospective Cohort</td>
<td>N=386 Patients admitted to the acute care brain injury unit at a Texas Hospital were enrolled in the study. Patients were administered either LMWH (30 mg/BID; N=158) or UFH (5000 IU sc/TID; n=171).</td>
<td>Those in the UHF had a higher rate of DVT and PE than those in the LMWH.</td>
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<tr>
<td>Koehler et al., (2011) USA</td>
<td>N=669 All patients were administered enoxaparin 30 mg s.c. every 12 hours. One group was given the medication &lt;72 hours</td>
<td>268 patients received DVT prophylaxis &lt;72 hours of admission, the remaining 401 were administered DVT prophylaxis &gt;/= 72</td>
</tr>
<tr>
<td>Study</td>
<td>Study Method</td>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Retrospective Cohort</td>
<td>Post hospital admission, the other &gt;/=72 hours post admission.</td>
<td></td>
</tr>
<tr>
<td>Scudday et al., (2011) USA Retrospective Cohort</td>
<td>N=812 Of these patients meeting the study inclusion criteria, 410 received not chemical prophylaxis therapy while 402 did. Ninety-one percent of patients received heparin while the remaining 9% were given enoxaparin.</td>
<td></td>
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<tr>
<td>Salottolo et al., (2011) USA Retrospective Cohort</td>
<td>N=480 Charts belonging to patients admitted to 2 Level 1 trauma facilities over a two year period were examined. Patients were placed on lovenox (30 mg of lovenox twice daily) or heparin (5000 U s.c.). The administration of chemical prophylaxis, its timing and where or not the treatment was interrupted was investigated. All patients were fitted with a sequential compression device.</td>
<td></td>
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<tr>
<td>Lu et al., (2011) USA Prospective control</td>
<td>N=282/81 patients were initially recruited into the study but only 81 were completed the study. Participants were administered 2.5 mg of fondaparinux subcutaneously. Those not candidates for DVT developed in 2 receiving fondaparinux. 6 DVTS were diagnosed in those wearing the stockings.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
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<tr>
<td>Kim et al., (2002) USA Cohort</td>
<td>N=76 Retrospective evaluation of severe closed head injury patients (Abbreviated Injury Scale Score &gt; 3) who received early unfractionated heparin (UFH). Intracranial bleeding associated to UFH administration was assessed by CT scan of the head and/or clinical examination. Two groups were formed based on timing of UFH administration: within 72 hours of admission (early group), or after the third day of hospitalization (late group).</td>
<td>There was no increase in intracranial bleeding or deterioration on neurological examination due to UFH administration. There was no statistical difference in venous thromboembolism events between the early and late groups.</td>
</tr>
<tr>
<td>Norwood et al., (2008) USA Case Series</td>
<td>N=525 Patients admitted to hospital for an ABI were placed on enoxaparin (30mg s.c. BID).</td>
<td>Of the 525 patients enrolled in the study, all were placed on enoxaparin approximately 36 hours post hospital admission. Of the 151 patients who underwent a lower extremity venous Doppler ultrasound, 6 patients were diagnosed with a DVT. No patient within the study group was diagnosed with a pulmonary embolism.</td>
</tr>
<tr>
<td>Kleindienst et al., (2003) USA and Germany Case Series</td>
<td>N=790 Retrospective evaluation of the records of a total of individuals undergoing elective neurosurgery (n=294), or admitted for head injury (n=344) or intracranial hemorrhage (n=302) included in this study. Prophylaxis was performed with certoparin (3000 U anti-factor Xa s.c.) on the evening prior to elective neurosurgery (ES) and within 24 hours after surgery or admission whenever a CT showed an absence of a progressive haematoma. The incidence of bleeding complications, venous thromboembolic events (VTE), and resulting morbidity/mortality was assessed.</td>
<td>Intracranial bleeding was found in 1.5% of patients. The incidence of VTE and pulmonary embolism was 0.2% and 0.1% of patients respectively, with no associated mortality. No heparin induced thrombocytopenia was observed.</td>
</tr>
<tr>
<td>Norwood et al., (2002) USA Pre-Post</td>
<td>N=150 ABI patients received enoxaparin (30 mg subcutaneous every 12 hrs beginning 24 hrs after initial evaluation in the emergency department). Progression of intracranial hemorrhagic injuries (IHI), mortality, and Glasgow Outcome Scale (GOS) at discharge were evaluated.</td>
<td>23% of patients had CT progression of IHI. Rate of progression of IHI significantly decreased after 24 hours from initiation of treatment (p = 0.002). Study group mortality was 7%. On the GOS scale, 76% (115/150) of patients showed good recovery, 7% (10/150) showed moderate disability, 9% (14/150) showed severe disability, and 1% showed no recovery.</td>
</tr>
</tbody>
</table>
Discussion

Several studies looking at the risk of administering chemical prophylaxis to prevent the development of DVTs post ABI were reviewed. In recent studies, results indicate that early treatment (within the first 72 hours) may reduce the risk of developing DVTs post injury (Kim et al., 2002; Salottolo et al., 2011; Scudday et al., 2011; Norwood et al., 2008) without increasing the risk of intracranial hemorrhagic injury (Koehler et al., 2011; Scudday et al., 2011).

Lu et al. (2011) studied the effect of fondaparinux on a group of TBI patients. 2.5 mg of fondaparinux was administered to patients once daily. Those who were not considered as candidates for the medication wore compression stockings. All underwent venous ultrasonography imaging of both the upper and lower extremities. Participants were monitored weekly throughout the study. Overall only 2 incidents of DVT were found, VTs or thrombocytopenia and patients did not experience any bleeding that could be attributed to the medication. These results suggest fondaparinux is safe and effective in protecting patients post injury from developing DVTS.

In a retrospective controlled trial, Kim et al. (2002) looked at differences between patients with ABI that received unfractionated heparin within three days of injury onset (n = 47) and those that received treatment later than three days post-injury (n = 17). Although there were no statistically significant differences between the groups in the number of thromboembolic events, it was noted that no patient in the early group experienced an increase in intracranial bleeding or deterioration on neurological examination.

Norwood and colleagues conducted two studies examining the benefits of administering enoxaparin prophylaxis to those who sustain a severe ABI within the first 48 hours post injury (Norwood et al., 2002; Norwood et al., 2008). Results from both studies indicate that administering enoxaparin post ABI reduces the risk of developing DVTs and PEs. It was also not found to increase the risk of bleeding post injury. Scudday et al. (2011) also found that patients who were administered 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.

Kleindienst et al.(2003) found that administering LMWH (certoparin) early post-surgery in patients who had sustained either an head injury or intracranial hemorrhage in combination with compression stocking was found to be associated with a 0.2% and 0.1% incidence rate of developing DVTs post injury. Again no significant increase in bleeding was noted as a result of administering the certoparin.
Despite the findings of these studies, to date there are no clear guidelines suggesting when to administer these medications post ABI. The Brain Trauma Foundation guidelines recommend using chemical prophylaxis (LMWH or heparin) until the patient is ambulatory (Elliot et al., 2006); however, injuries to the lower extremities would preclude this. To date the lack of quality controlled studies, make it difficult to really assess when these medication should be administered.

Conclusions

There is Level 2 evidence supporting the administration of LMWH within the first 72 hours post ABI to reduce the risk of developing DVTs and PEs post injury.

There is Level 2 evidence supporting the administration of fondaparinux in patients who have sustained a TBI.

There is Level 2 evidence that administering LMWH (enoxaparin) or heparin post ABI does not increase the risk of intracranial bleeding.

Although the administration of chemical prophylaxis within the first 72 hours post ABI has been shown to be effective in reducing the risk of developing DVTs or PEs without increasing the risk of intracranial bleeding more research is needed to determine its true effectiveness.

Fondaparinux has been shown to be effective in the prevention of DVTs post TBI.

Enoxaparin is effective for the prevention of VT after elective neurosurgery and has not been found to cause excessive bleeding.

11.8.2 LMWH vs Low-Dose Heparin

Subcutaneous heparin in low doses has been reported to be both safe and efficient (Watanabe & Sant, 2001). The route of delivery may also affect the efficacy of anticoagulant prophylaxis (Watanabe and Sant 2001). In this regard intravenously delivered heparin may be more efficient in the prevention of thromboembolism compared with subcutaneous administration, although this method of delivery might increase the risk of bleeding (Green et al., 1988). Low-molecular weight heparins, which are injected subcutaneously, are also gaining 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 and Sant 2001). Carlile et al. (2006) found that 15 of the 16 rehabilitation centers surveyed reported routinely initiating treatment with either LMWH or low-dose unfractionated heparin.
Individual Studies

Table 11.7 LMWH vs Low-Dose Heparin

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Geerts et al., (1996) USA RCT PEDro = 7</td>
<td>N=344 Consecutive adult patients admitted to a trauma center with Injury Severity Scores of at least 9 and no intracranial bleeding were randomized to heparin (5000 units) or enoxaparin (30 mg), administered subcutaneously every 12 hours in a double blind manner, starting within 36 hours post injury. The main outcome was deep-vein thrombosis (DVT) as assessed by contrast venography, which was measured on or before day 14 post randomization.</td>
<td>136 patients randomized to low-dose heparin and 129 randomized to enoxaparin had venograms adequate for analysis. 60 patients given heparin (44%) and 40 patients given enoxaparin (31%) suffered a DVT (P=0.014). There was a 30% (95% CI, 4 to 50 percent) reduction in risk with enoxaparin administration compared with heparin for all DVT and 58% (95% CI, 12 to 87 percent) for proximal-vein thrombosis. Only 6 patients (1.7%) had major bleeding (one from heparin group and five from enoxaparin group, P=0.12).</td>
</tr>
</tbody>
</table>

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Geerts et al. (1996) explored the use of low-dose heparin for the treatment of DVT as well as the use of enoxaparin (low-molecular weight heparin). Of those receiving low-dose heparin 44% suffered a DVT compared to 31% of patients receiving enoxaparin (low molecular weight heparin).

Conclusion

There is Level 1b evidence that low-molecular-weight heparin is more effective than low-dose unfractionated heparin in preventing venous thromboembolism after severe trauma.

Low molecular weight heparin is more effective than low dose heparin in preventing venous thromboembolism after severe trauma.
11.8.3 Combination Treatments

Compression stockings and pneumatic compression devices are the major strategies used for the prevention of mechanical DVT in trauma patients (Watanabe and Sant 2001). Such mechanical methods are generally more advisable than the use of anticoagulants due to the concomitant increased risk of bleeding in patients with multiple fractures and injuries (Watanabe and Sant 2001). These mechanical strategies have demonstrated positive results in the prophylaxis of DVT in neurosurgical patients (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. For example, Agnelli et al. (1998) reported an additive reduction in thromboembolism, without a significant increase in bleeding risks, in patients treated with both enoxaparin and a compression stocking compared with patients treated with mechanical compression alone.

Another method of mechanical DVT prevention is the vena cava filter (Watanabe and Sant 2001). These filters are inserted into the inferior vena cava to prevent the passage of emboli into the lungs. Some reports have demonstrated success rates as high as 96% in the prevention of pulmonary emboli (Greenfield & Michna, 1988). However, the use of vena cava filters also carry some associated risks. They can become blocked or dislodged, which can both increase the risk of an embolism. Some have also reported increased risks for repeated DVT in patients with vena cava filters compared with patients without such devices (Decousus et al., 1998).

Individual Studies

Table 11.8 Physical and Pharmaceutical Methods to Treat DVTs post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design/PEDro Score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agnelli et al., (1998) USA RCT PEDro = 6</td>
<td>N=307 Individuals were randomized to receive enoxaparin (40 mg once daily) or placebo administered subcutaneously for no less than seven days beginning within 24 hours post elective neurosurgery. All patients were fitted with thigh-length compression stockings which were patients wore from the morning of surgery until discharge.</td>
<td>129 of the 154 patients receiving placebo (84%) and 130 of the 153 patients receiving enoxaparin (85%) had venographic studies sufficient for analysis. 42 patients in the placebo group (32%) and 22 patients in the enoxaparin (17%) group had DVT. The rates of proximal DVT were 13% in patients taking placebo and 5% in patients taking enoxaparin. Major bleeding took place in 4 patients receiving placebo and 4 patients receiving enoxaparin.</td>
</tr>
<tr>
<td>Decousus et al., (1998)</td>
<td>N=400 Those with proximal DVT who were at risk for pulmonary embolism</td>
<td>At day 12, 3 patients assigned to low-molecular-weight heparin (1.6%), as</td>
</tr>
</tbody>
</table>
**Author/Year/Country/Study design/PEDro Score** | **Methods** | **Outcome**
--- | --- | ---
USA RCT PEDro = 6 | were randomized to receive a vena cava filter (200 patient) or no filter (200 patients), and to receive low-molecular-weight heparin (enoxaparin, 195 patients) or unfractionated heparin (205 patients). Rate of recurrent venous thromboembolism, death, and major bleeding were analyzed at day 12 and two years. | compared with 8 patients receiving unfractionated heparin (4.2%), had symptomatic or asymptomatic pulmonary embolism (95% CI, 0.10-1.38). At two years, 37 patients in the filter group (20.8%) vs. 21 patients in the no-filter group (11.6%), had recurrent deep-vein thrombosis.

**Kurtoglu et al., (2004) Turkey Prospective control** | N=120 A combination of ABI (85% n=102), spinal cord injury and stroke patients received either Intermittent Pneumatic Compression Devices (IPC) or Low-Molecular-Weight Heparin (LMWH) for venous thromboembolism prophylaxis. The patients in the IPC group were placed on below the knee IPC devices. Patients in the LMWH group received 40mg/day of enoxaparin sodium. The incidence of DVT, PE and mortality rates were compared. | There were no significant differences between groups in pulmonary embolisms, deep vein thrombosis and mortality rates (p=0.04, p=0.07, p=0.08 respectively).

**Velmahos et al., (1998) USA Case Series** | N=200 Critically ill patients (n=52 with Head Trauma) at high risk for DVT were assigned to receive sequential compression devices (SCD) ± low dose heparin (LDH). Patients were followed by weekly Doppler examinations to detect DVT at the proximal lower extremities. SCD were applied to 97.5% of the patients, LDH was administered to 46% of subjects, and 45% received both treatments. | DVT was found in 26 patients (13%), with the majority (58%) developing DVT within the first 2 weeks. However, new cases were found as late as 12 weeks post admission. The incidence of DVT was the same for patients who had SCD only or a combination of LDH and SCD. Patients who developed DVT stayed longer in the ICU than those who did not (34 ± 31 vs. 19 ± 18 days respectively, p<0.05).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

**Discussion**

Four studies investigating the benefits of using compression stockings and medication to prevent or treat DVTs post ABI were reviewed. In one study Decousus et al. (1998) randomly assigned 400 patients to receive either a vena cava filter or not, and to receive low molecular weight heparin (enoxaparin) or unfractionated heparin. At time of measurement (day 12), 1.6% of patients assigned to receive low-molecular-weight heparin had a symptomatic or asymptomatic PE, compared with 4.2% of patients receiving unfractionated heparin. There were no statistically significant differences between the two groups when looking at major internal bleeding episodes. Patients
assigned to the vena cava filter group were found to develop fewer symptomatic or asymptomatic pulmonary emboli than those in the no filter group.

In a second RCT, conducted by Agnelli et al. (1998) patients undergoing elective neurosurgery, were placed on low-molecular weight heparin or a placebo 24 hours prior to neurosurgery. All patients were also fitted with combination compression stockings. Venography studies were conducted on 84% of participants. Results indicate that more in the placebo group developed DVTs than in the treatment group (p<0.004). Thirteen percent of those in the control group developed proximal DVTs compared to 5% of the treatment group (p=0.04).

In another study conducted by Kurtoglu et al. (2004), 120 patients were allocated to receive either an intermittent pneumatic compression device or low-molecular weight heparin (enoxaparin) prophylactically for the prevention of venous thromboembolism. The authors reported that there were no significant differences between groups in the development of pulmonary embolism, deep vein thrombosis, or in mortality rates. Although this study did not include a control group the results suggest that sequential compression devices are as effective as enoxaparin for the prevention of DVT.

In contrast to these finding, another study looking at the risk of developing DVTs among patients who wore sequential compression devices (SCDs) only and those who wore SCDs and were given low-dose heparin (LDH), no differences were found in the between the two groups (Velmahos et al., 1998). The administration of LDH and wearing a SCD was not any more effective in preventing the development of DVTs post injury. Overall DVTs developed in 26 of the 200 patients in the study. Fifty-eight percent of the DVTs were found within the first two weeks of injury (Velmahos et al., 1998).

Conclusions

There is Level 1b evidence suggesting that low-molecular-weight heparin is as effective and safe as unfractionated heparin for the prevention of pulmonary embolism.

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 do not cause excessive bleeding.

There is Level 2 evidence that intermittent pneumatic compression devices alone are as effective as low molecular weight heparin for the prevention of DVT in ABI patients.

There is Level 4 evidence that a combination of low-dose heparin and sequential compression devices (SCDs) demonstrate no advantage over SCDs alone in reducing DVT rates in critically ill patients.
Low molecular weight heparin is as effective and safe as unfractionated heparin for the prevention of pulmonary embolism.

A combination of low dose heparin (LDH) and sequential compression devices (SCDs) demonstrated no advantage over SCD alone in reducing DVT rates in critically ill patients.

11.8.4 Mechanical Interventions to Prevent DVTs Post ABI

Mechanical interventions used to prevent the development of DVTs post ABI include: the insertion of vena cava filters, thromboembolism deterrent stocking, intermittent pneumatic compression devices including arteriovenous foot pumps and SCDs. There are two mechanism of action for these mechanical devices. First the mechanical: as the velocity of venous return is increased there is a decrease in venous stasis. Second is the activation of the fibrinolytic system. During compression, plasminogen activators are released (Macatangay et al., 2008). The findings of Camerota et al. (1992) also suggest that these mechanical strategies are often not used appropriately in both acute and nursing care settings, thus diminishing their prophylactic potential. To increase the effectiveness of these devices, compliance is absolutely necessary.

Individual Studies

Table 11.9 Mechanical Interventions used to Prevent DVTs post ABI

<table>
<thead>
<tr>
<th>Author/Year/Country/Study design</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gersin et al., (1994) USA Cohort</td>
<td>N=32 Patients who had sustained a severe TBI (GCS≤8) were included in the current study. 14 patients received prophylactic SCDs and while the remaining 18 did not.</td>
<td>Of those who were given SCD prophylaxis 4 developed PE but not developed a DVT. Of the remaining 18, those who did receive a SCD, 2 developed a PE or DVT. No statistically significant differences were found between the two groups (p=0.7).</td>
</tr>
<tr>
<td>Davidson et al., (1993) USA Pre-Post</td>
<td>N=24 Severe ABI patients (mean GCS of 6, median score of 3) received intermittent sequential pneumatic leg compression devices (6 series of compartments inflated serially with an 11 sec compression phase followed by 60 sec of deflation) for the prevention of venous thrombosis.</td>
<td>Mean arterial pressure (MAP), heart rate, central venous pressure, and intracranial pressure at 0, 10, 20 and 30 min after intermittent pneumatic leg compression were assessed. No significant changes in MAP, central venous pressure, or intracranial pressure during the study period (p&lt;0.05).</td>
</tr>
</tbody>
</table>
Discussion
Gersin et al. (1994) investigated the effectiveness of sequential compression devices (SCDs) in 32 patients who had suffered a severe TBI. Of these 32 patients 14 wore the devices, while the remaining 18 acted as the control group. Of the 14 who wore SCDs, no DVTs were noted, but 4 were found to develop a PE. In the remaining 18 patients, 2 developed a PE and 2 developed a DVT. Statistically there were no significant differences between the two groups.

Davidson et al. (1993) conducted a study to evaluate the possibility that intermittent pneumatic compression could aggravate intracranial hemodynamics in severe brain injury patients. 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 reason to contraindicate the acute use of pneumatic compression for the prevention of DVT in severe brain injury patients who are responsive to conventional intracranial management measures.

Conclusions
There is Level 2 evidence from one small study to suggest that SCD are not entirely effective in reducing the risk of developing a DVTs or PEs post ABI.

There is Level 4 evidence that intermittent compression devices do not aggravate acute elevations in intracranial pressure in severe ABI patients.

SCDs do not reduce the risk of developing DVTs or PEs post ABI.

Intermittent compression devices do not aggravate intracranial hemodynamics in severe ABI patients.

Overall Conclusions
The evidence tends to favor prophylactic anticoagulation, which reduces the risk of suffering a DVT without increasing the risk of intracranial bleeding. Low-molecular weight heparin used prophylactically appears to be more effective in preventing DVTs without causing increased risk of intracranial bleeding. Unfortunately, due to the limited amount of research available that is directly related to the development of DVTs post ABI, the decision to begin pharmacological prophylaxis post ABI remains a subjective one (Norwood et al., 2008).
11.9 Summary

1. The pathophysiology of heterotopic ossification is not fully established.

2. 10 – 20% of TBI patients develop heterotopic ossification. The hips, shoulders and elbows are most commonly affected. Clinical features include warm, swollen painful joint with some restriction of ROM.

3. There is Level 4 evidence that forceful manipulation under general anesthesia increases range of motion in patients with heterotopic ossification following brain injury.

4. There is Level 5 (very limited) evidence that continuous passive motion reduces the development of heterotopic ossification in severe head injury patients.

5. There is Level 2 evidence that etridonate (EHDP) reduces the development of heterotopic ossification in severe head injury patients.

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

7. There is Level 2 evidence supporting the administration of LMWH within the first 72 hours post ABI to reduce the risk of developing DVTs and PEs post injury.

8. There is Level 2 evidence supporting the administration of fondaparinux in patients who have sustained a TBI.

9. There is Level 2 evidence that administering LMWH (enoxaparin) or heparin post ABI does not increase the risk of intracranial bleeding.

10. There is Level 1b evidence that low-molecular-weight heparin is more effective than low-dose unfractionated heparin in preventing venous thromboembolism after severe trauma.

11. There is Level 1b evidence suggesting that low-molecular-weight heparin is as effective and safe as unfractionated heparin for the prevention of pulmonary embolism.

12. 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 does not cause excessive bleeding.
13. There is Level 2 evidence that intermittent pneumatic compression devices alone are as effective as low molecular weight heparin for the prevention of DVT in ABI patients.

14. There is Level 4 evidence that a combination of low-dose heparin and sequential compression devices (SCDs) demonstrate no advantage over SCDs alone in reducing DVT rates in critically ill patients.

15. There is Level 2 evidence from one small study to suggest that SCD are not entirely effective in reducing the risk of developing a DVTs or PEs post ABI.

16. There is Level 4 evidence that intermittent compression devices do not aggravate acute elevations in intracranial pressure in severe ABI patients.
11.10 Reference List


Crawford CM, Varghese G, Mani MM, Neff JR. Heterotopic ossification: are range of motion exercises contraindicated? J Burn Care Rehabil 1986; 7: 323-327


