6.1 Dysphagia

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6.1.1 Normal Swallowing

Consists of 4 Phases:

Oral Preparatory Phase
Food in oral cavity is manipulated and masticated in preparation for swallowing. The back of the tongue controls the position of food, preventing it from falling into pharynx.

Oral Propulsive Phase
The tongue elevates and occludes the anterior oral cavity. The tongue then compresses the bolus toward the oropharynx. This then triggers the pharyngeal swallow. Problems at this stage lead to drooling and pocketing.

Pharyngeal Phase
This is the most important phase and involves complex and coordinated movements of the tongue and pharyngeal structures propel the food bolus into the esophagus while protecting the airway. This is largely a reflex action. Aspiration is most likely to occur during this phase. This phase also requires soft palate elevation and velopharyngeal port closure to prevent regurgitation into oropharynx. Laryngeal elevation with folding of epiglottis and vocal cord adduction serves to prevent aspiration along with coordinated pharyngeal constriction and cricopharyngeal relaxation. Difficulties at this stage are characterized by choking, coughing and aspiration.
Esophageal Phase
This is the final phase and involves coordinated contractions of the esophagus muscle move the bolus through the esophagus toward the stomach.

Definitions of Abnormal Swallowing Post-Stroke
- Dysphagia = difficulty with swallowing.
- Penetration = entry of material into the larynx but not below the true vocal cords.
- Aspiration = entry of material into airway below level of true vocal cords.

6.1.2 Dysphagia Post-Stroke
Dysphagia post stroke is very common. Finestone et al. (1995) found 47% of rehab admissions had dysphagia, 49% were clinically malnourished. Dysphagia can lead to malnutrition and dehydration. Malnutrition is associated with worse functional outcomes. Dysphagia is associated with aspiration.

Signs and Symptoms of Dysphagia
- Choking on food.
- Coughing during meals.
- Drooling or loss of food from mouth.
- Pocking of food in cheeks.
- Slow, effortful eating.
- Difficulty swallowing pills.
- Avoiding foods or fluids.

Think dysphagia when patient is complaining of:
1. Food sticking in throat.
2. Difficulty controlling liquids and saliva.
3. Problems swallowing.
4. Reflux or heartburn.

6.1.3 Aspiration Post-Stroke
Prospective studies of acute strokes (< 5 days) show 21%-42% aspirate earl on. Aspiration rate improves to 8%-15% at 3 months post stroke.

Pneumonia Post-Stroke
The diagnosis of pneumonia varies with the criteria used and population group studied. This accounts for the wide reported variance in older studies with 7% - 32% incidence reported in the acute stroke population. More recent and more aggressive management of dysphagia has made pneumonia much less common in stroke patients. Previously up to 20% of individuals with stroke-related dysphagia died during the first year post-stroke of aspiration pneumonia but this has dramatically improved with aggressive management of dysphagia.
Association of Dysphagia or Aspiration and Pneumonia Post-Stroke

Aspiration alone does not lead to pneumonia. Aspiration of small amounts of saliva during sleep occurs in ½ of elderly. Pneumonia is likely to occur when the lung’s natural defenses are overwhelmed by excessive or toxic aspirate.

Relationship between Dysphagia and Pneumonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of Pneumonia Among Patients with and without Dysphagia</th>
<th>OR (95% CI, fixed effects model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al. 1987</td>
<td>7/37 vs. 4/50</td>
<td>2.63 (0.72 to 9.96)</td>
</tr>
<tr>
<td>De Pippo et al. 1994</td>
<td>10/82 vs. 1/57</td>
<td>7.78 (0.97 to 62.6)</td>
</tr>
<tr>
<td>Gottlieb et al. 1996</td>
<td>9/50 vs. 9/130</td>
<td>2.95 (1.10 to 7.94)</td>
</tr>
<tr>
<td>Smithard et al. 1996</td>
<td>20/60 vs. 9/57</td>
<td>2.67 (1.09 to 6.50)</td>
</tr>
<tr>
<td>Reynolds et al. 1998</td>
<td>18/69 vs. 3/33</td>
<td>3.53 (0.96 to 12.99)</td>
</tr>
<tr>
<td>Teasell et al. 2002</td>
<td>5/11 vs. 0/9</td>
<td>-</td>
</tr>
<tr>
<td>Falsetti et al. 2009</td>
<td>1/89 vs. 8/62</td>
<td>13.04 (1.44 to 286)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>70/398 vs. 34/398</td>
<td>2.28 (1.44 to 3.61)</td>
</tr>
</tbody>
</table>

Comparison of Pneumonia Frequency in Stroke Patients between Dysphagia and Non-Dysphagia

<table>
<thead>
<tr>
<th>Study</th>
<th>Dysphagic n/N</th>
<th>Non-Dysphagic n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al. 1987</td>
<td>7/37</td>
<td>4/50</td>
<td>14.09 (6.95, 25.84)</td>
<td>34.68</td>
<td>2.36 (1.36, 3.61)</td>
</tr>
<tr>
<td>De Pippo et al. 1994</td>
<td>10/82</td>
<td>1/57</td>
<td>4.98 (2.97, 8.41)</td>
<td>18.24</td>
<td>6.95 (4.91, 9.64)</td>
</tr>
<tr>
<td>Gottlieb et al. 1996</td>
<td>9/50</td>
<td>9/130</td>
<td>3.57 (2.11, 6.27)</td>
<td>23.34</td>
<td>2.00 (1.24, 3.22)</td>
</tr>
<tr>
<td>Smithard et al. 1996</td>
<td>20/60</td>
<td>5/77</td>
<td>3.13 (1.77, 5.49)</td>
<td>23.34</td>
<td>6.95 (4.40, 10.57)</td>
</tr>
<tr>
<td>Reynolds et al. 1998</td>
<td>18/69</td>
<td>3/29</td>
<td>3.57 (2.11, 6.27)</td>
<td>23.34</td>
<td>6.95 (4.40, 10.57)</td>
</tr>
<tr>
<td>Mann et al. 1999</td>
<td>24/110</td>
<td>2/110</td>
<td>3.57 (2.11, 6.27)</td>
<td>23.34</td>
<td>6.95 (4.40, 10.57)</td>
</tr>
<tr>
<td>Daniels et al. 2000</td>
<td>6/86</td>
<td>6/34</td>
<td>1.77 (0.97, 3.24)</td>
<td>13.04</td>
<td>6.95 (4.40, 10.57)</td>
</tr>
<tr>
<td>Toselli et al. 2002</td>
<td>5/11</td>
<td>6/9</td>
<td>2.72 (0.97, 7.07)</td>
<td>13.04</td>
<td>6.95 (4.40, 10.57)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>492 (Dysphagic)</td>
<td>520 (Non-Dysphagic)</td>
<td>2.28 (1.44, 3.61)</td>
<td>100.00</td>
<td>3.07 (1.93, 4.88)</td>
</tr>
</tbody>
</table>

Risk Factors Associated with Aspiration Difficulties Post-Stroke

- Brainstem stroke.
- Difficulty swallowing oral secretions.
- Coughing/throat clearing, choking or wet gurgly voice quality after swallowing water.
- Weak voice and cough.
- Recurrent lower respiratory infections.
- Aspiration or pharyngeal delay on VMBS.
- Immunologically compromised or chronic lung disease.
- Poor oral hygiene.
6.1.4 Management of Dysphagia and Aspiration Post-Stroke

Goals of Dysphagia Management
- Meet the nutritional and hydration needs of the stroke survivor.
- Prevent aspiration-related complications.
- Maintain and promote swallowing function as much as possible.

Initial Management
Acute stroke survivors should be maintained NPO until their swallowing ability is determined. Clinical bedside screening is conducted by a trained team member. Need to carefully monitor hydration and nutritional status.

Initial Bedside Assessment
- Risk factors (see above) should alert the clinician to carefully assess for dysphagia.
- Oral motor assessment usually by speech language pathologist.
- Trial of 1-2 teaspoons of water.
- Followed by small cup of water.
- Choking, coughing or wet gurgly voice are all suggestive of aspiration.

Efficacy for Clinical Screening of Dysphagia
Clinical screening tests have been compared to VMBS studies and health outcomes. Only two clinical screening tests found correlations with the findings of VMBS: 1) failure on 50 ml water test and 2) impaired pharyngeal sensation (Miles et al. 2003; Sorensen et al. 2013). There is limited evidence that clinical screening of dysphagia reduces pneumonia or length of hospital stay although it is considered standard of care.

Silent Aspiration Post-Stroke
Silent aspiration is defined as passage of food below level of true vocal cords without cough or outward sign of difficulty. 8%-26% of aspirators acutely are silent aspirators (within the first 5 days post stroke). Reliability of clinical assessment can be uncertain because of the risk of silent aspiration resulting in increasing reliance on VMBS studies to definitively rule out aspiration, particularly in higher risk patients.

Video-fluroscopic Modified Barium Swallow (VMBS)
VMBS is considered the “gold standard” for the diagnosis of aspiration. VMBS allows direct visualization of swallowing function in the oral and pharyngeal phases. It allows diagnosis of the degree of aspiration and whether it is silent or accompanied by a cough or throat clearing.

For a VMBS, the patient must be able to perform the test. Radio-opaque thin and thick fluids; pudding, bread, and cookies laden with barium are routinely used. Various aspects of oral and pharyngeal movements and coordination of bolus are observed as is presence and degree of aspiration. Based on anecdotal experience and clinical associations, the greater the degree of aspiration, the greater the risk of pneumonia, which makes intuitive sense. Aspiration of >10% of bolus or severe pharyngeal motility problems on VMBS are regarded as high risk of developing pneumonia. VMBS does result in x-ray radiation exposure.
Benefit of VMBS Studies in Stroke

• Establishes the presence and extent of aspiration.
• Reveals abnormal mechanics: reduced laryngeal closure and/or pharyngeal paresis, etc.
• Demonstrates efficacy of compensatory techniques.
• Allows for tracking of the progression of aspiration risk.

Indication for VMBS Studies

• Brainstem stroke.
• Obvious signs of choking or wet, hoarse voice after drinking.
• Problems maintaining adequate nutrition and hydration.
• Recurrent respiratory infections.
• Follow-up of previous positive VMBS study.

Figure. Anatomy of the Pharynx showing the Valleculae and Piriformis Sinuses where barium can pool in patients with dysphagia and at risk of aspiration

Figure. Anatomy of the Pharynx and Trachea and evidence of pooling in the Valleculae and Piriformis Sinuses as well as Aspiration of Barium (below the level of the true vocal cords)
Flexible Endoscopic Evaluation of Swallow (FEES)
FEES is an increasingly available, rapid, bedside assessment of swallow allowing direct visualization of true vocal cords. It need to be performed by an trained team member. In this diagnostic test, an endoscope is passed through one nostril and a camera is placed at the laryngeal opening. The camera view blocked during actual swallow but able visualize cords before and after the swallow and assess vocal cord mobility. A common complaint from patients is that presence of the camera interferes with bolus manipulation during oral and phalangeal phases of swallow.

6.1.5 Treatment of Dysphagia

Dietary Modifications
The evidence that dietary modifications affects the risk of aspiration pneumonia is not well established in stroke but is well accepted. Generally foods with a variety of consistencies are tried: Solids: puree, minced, chopped, soft and regular, Liquids: pudding, honey, nectar and thin. The proper consistency of food or diet is dictated by VMBS studies and clinical assessment. Thin liquids are typically harder to manage than pudding thick, regular solids are harder to manage than puree diet. Thick fluids or even jelled water are used to eliminate thin liquids when this consistency proves hard to manage. Dysphagia soft diet eliminates all hard, small, and stringy food particles. Sequential VMBS in complicated cases allows for progression of diet with swallowing recovery.

Low-Risk Feeding Strategies
It is important to encourage stroke survivors to feed themselves as the risk of aspiration pneumonia increases 20 fold when they are fed by someone else, generally because they eat at too fast a rate. Feed with hand-over-hand support at eye level if necessary. Postural feeding strategies include chin tuck, head tilt, etc. Guidelines for low risk feeding strategies are listed below.


• Check the food tray to ensure the correct diet type has been provided.
• Ensure the environment is calm during meals and minimize distractions.
• Position the stroke survivor with the torso at a 90° angle to the seating plane, aligned in mid-position with the neck slightly flexed.
• Support the stroke survivors with pillows if necessary.
• Perform mouth care before each meal to remove bacteria that have accumulated on the oral mucosa.
• Feed from a seated position, so that you are at eye level with the stroke survivor.
• Do not use tablespoons. Use metal teaspoons, never plastic for feeding individuals with bite reflexes.
• Use a slow rate of feeding and offer a level teaspoon each time.
• Encourage safe swallowing of liquids by providing them with wide-mouth cup or glass or in a cut-down nosey cup, which helps prevent the head from flexing backward and reduces the risk of aspiration. Some individuals may benefit from drinking through a straw.
• Ensure that swallowing has taken place before offering any additional food or liquid.
• Observe the stroke survivor for any signs or symptoms of swallowing problems during and for 30 minutes after the meal.
• Perform mouth care after each meal to ensure that all food debris is cleared from the mouth.
• Position the patient comfortably upright for at least 30 minutes after each meal to promote esophageal clearance and gastric emptying and to reduce reflux.
• Monitor the oral intake of the stroke survivor with dysphagia: note any food items that are not consumed and ensure that intake is adequate, especially important in individuals receiving a thickened-liquid diet.
• Document the patient’s intake, any changes in swallowing status and any self-feeding problems.

Compensatory Strategies
There are a number of compensatory strategies for the stroke patient with dysphagia which are thought to reduce the risk of aspiration. Patients should be fed in the upright posture. Chin tuck facilitates forward motion of the larynx, thereby preventing food material from entering into the larynx and reducing the space between the base of the tongue and the posterior pharyngeal wall increasing pharyngeal pressure on bolus moving through the pharynx. Head rotation to the paretic side closes the ipsilateral pharynx, forces the bolus into the contralateral, less affected side of the pharynx and decreases cricopharyngeal pressures. Head tilt uses gravity to guide the bolus into the ipsilateral pharynx. Supraglottic swallow involves concomitant breath holding and swallowing which closes the tracheal vocal cords to protect the trachea. Supersupraglottic swallow adds the Valsalva maneuver to maximize vocal fold closing. Double swallowing and coughing after swallowing helps to protect the airway. Close supervision with cueing may be required to slow down impulsive fast eaters, especially right hemispheric stroke patients.

Transcutaneous Electrical Stimulation
There is conflicting evidence that neuromuscular electrical stimulation of pharyngeal muscles improves swallowing function.

Repetitive Transcranial Magnetic Stimulation
There is strong evidence that rTMS may improve aspiration, swallowing function and functional disability when compared to sham stimulation.
Non-Oral Feedings

Non-oral feeding is a well-established practice for those patients who cannot handle oral feeds. Non-oral feedings can be implemented almost immediately following a stroke in high risk patients using a naso-gastric tube. If dysphagia is severe (i.e. patient is still aspirating in rehabilitation despite dietary modifications and compensatory strategies) and is expected to continue to do so for more than 6 weeks, a gastrostomy or jejunostomy tube is necessary. The FOOD study (Dennis et al. 2005) found that starting enteral feeds had a positive impact on post stroke recovery but that GI or jejunostomy tube placement should be postponed for 4 weeks due to morbidity associated with the procedure with no difference in complications when compared to NG tube. Jejunostomy tubes are theoretically better than gastrostomy tube in aspirators, because of less risk of reflux. Complications are manageable.
Stroke Rehabilitation Clinician Handbook

Figure. Assessment of Swallowing Post Stroke at Time of Admission

Clinical Swallowing Assessment

Clinical Risk Factors (at least one):
• Brainstem Stroke.
• Choking more than once while drinking 50cc of water.
• Difficulty swallowing oral secretions.
• Coughing/throat clearing or wet, gurgly voice quality after swallowing water.
• Weak voice and cough.
• Recurrent lower respiratory infections.

Yes

VMBS

Minimal Aspiration
(< 10 % of test bolus)

Dietary Modification and Feeding Strategies

No Aspiration

Regular Diet

No

Gross Aspiration
(> 10 % of test bolus)

Enteral Tube Feedings
Figure. Continuing Management of Minimal Aspiration

Minimal Aspiration (<10% of test bolus on VMBS)

Clinical Swallowing Assessment

- Improved → Upgrade Diet Modifications
- Not Improved (4-12 weeks)

Repeat VMBS

- Negative for Aspiration → Regular Diet
- Minimal Aspiration (<10% of test bolus) → Continue or Upgrade Dietary Modifications/Feeding Strategies
Figure. Management of Gross Aspiration

Gross Aspiration

After 4-8 weeks

Repeat VMBS

Negative for Aspiration

Gross Aspiration (> 10% of test bolus)

Continue Enteral Feeding

Regular Diet

Dietary Modifications and Feeding Strategies

Minimal Aspiration (< 10% of test bolus)
6.2 Nutrition Post-Stroke

6.2.1 Malnutrition in Stroke

Malnutrition increases while the stroke patient is in hospital. 50% of severe strokes have been reported to be malnourished at 3 weeks post-stroke onset and this improves to 20% among rehabilitation patients at 2-4 months.

Complications of Malnutrition Post-Stroke
Malnutrition is associated with:
1. Lower Barthel Index scores at 1-4 months.
2. Increased length of stay.
3. Greater risk of bedsores and UTIs.
4. Decreased response to physiotherapy.

6.2.2 Body Mass Index (BMI)

BMI or body mass index is often used to estimate whether a person is underweight, normal weight or overweight. While there are limitations associated with the use of BMI to detect overweight or obese individuals, it is useful to help quickly identify those who are underweight and may be malnourished.

\[
\text{BMI} = \frac{\text{Weight \ [in \ kilograms]}}{(\text{Height \ [in \ meters]})^2}
\]

BMI=47/1.60²
BMI= 18.4

There are many interpretations of BMI although values between 18.5 and 24.9 are considered optimum by most professionals. A BMI of 25 to 29.9 is considered overweight and one 30 or above is considered obese. A value less than 19.5 is considered to be underweight.

6.3 Venous Thromboembolism Post Stroke

6.3.1 Deep Venous Thromboembolism Post-Stroke

Virchow’s Triad describes the three major risk categories for thrombosis that contribute to venous thromboembolism. These are:

1. Hypercoagulability
2. Hemodynamic changes (stasis/turbulence)
3. Endothelial injury

Following stroke the main risk factor is immobilization resulting in stasis of venous blood. Hypercoagulability may also contribute in certain subsets of stroke patients.
Clinical
In the absence of prophylactic treatment, 50 – 75% of dense hemiplegics develop a DVT while 9 – 15% will have a pulmonary emboli and 1 – 2% will be fatal. The incidence of DVTs may be as high as 45% (many are asymptomatic) in acute phase but falls to < 10% of subacute rehabilitation. The peak onset is 2-7 days post stroke. Venous thromboembolism usually begins with calf DVT. Most of these are asymptomatic but 5 – 10% are symptomatic. Untreated, 20% of distal calf DVTs will extend into the proximal veins. When DVT causes symptoms, over 80% involve the popliteal or more proximal veins; symptomatic DVTs are rarely isolated distal calf DVTs. Non-extending distal (calf) DVT rarely causes PE; proximal (knee or above) DVT often causes PE. Isolated distal calf DVTs extend proximally over one week. Clinically symptomatic DVTs are less common in subacute (rehab) phase. The odds of DVT are 17.6X greater if the patient is bedridden or wheelchair bound.
Pulmonary Emboli Post-Stroke
Pulmonary emboli are quite common post-stroke. Most are asymptomatic or unrecognized. Symptomatic PEs are large.

6.3.2 Diagnosis of DVT

Clinical Model of DVT
If any of the following are present score one point:
1. Active cancer
2. Paralysis, paresis or recent plaster immobilization of L/E
3. Recently bedridden > 3 days or major surgery within 4 weeks
4. Localized tenderness along the distribution of the deep venous system
5. Entire leg swollen
6. Calf swelling 3 cm > asymptomatic side
7. Pitting edema confined to the symptomatic leg
8. Dilated superficial veins (non-varicose)

Subtract 2 points if there is an alternative diagnosis as or more likely than DVT.

The Likelihood of having a DVT

<table>
<thead>
<tr>
<th>Probability</th>
<th>Total Points</th>
<th>Prevalence of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>85%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 or 2</td>
<td>33%</td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>5%</td>
</tr>
</tbody>
</table>

Venous Ultrasound
Venous ultrasound have a sensitivity of 95% and is diagnostic in almost all patients with symptomatic proximal DVT. Specificity of venous ultrasound is 96% which means it is normal in almost all patients with leg symptoms but no DVT. Sensitivity is 73% for distal calf DVTs. The majority of symptomatic distal DVTs that extend do so within a week. Serial testing may be used if he test is negative but the patient is symptomatic; it will become positive if it extends proximally.

D-dimer Assays
D-dimer assays are a rapid, non-invasive and inexpensive test. Fibrin is the main component of thrombus formation; fibrin degradation products include d-dimers. D-dimers are frequently found in the blood when venous thromboembolism is present. The positive d-dimer test is very sensitive but lacks specificity since d-dimers are also found in other disease states including cancer, congestive heart failure, and inflammatory conditions. D-dimers assays have a high negative predictive value, i.e. when it is negative you can relax (sensitive). D-dimers assays have a poor positive predictive value, i.e. when it is positive it could be something else and you don’t know if it is VTE (not specific).
Figure. Degradation of Fibrinogen

Positive Diagnosis for DVT
A positive venous ultrasound at two or more sites proximal veins is needed for a positive diagnosis of a DVT.

Negative Diagnosis for DVT
A negative diagnosis for DVT include:

- Negative D-dimer test
- Normal venous ultrasound and
  - low clinical suspicion for DVT, or
  - normal D-dimer test, or
  - normal serial testing (repeat testing one week later)

6.3.3 Diagnosis of Pulmonary Emboli

The clinical diagnosis of a pulmonary embolus is unreliable being both insensitive and non-specific. Many cases of pulmonary emboli are clinically silent with only 30% having clinical features of a DVT and 70% DVT on venography.

Massive Pulmonary Embolus
Patients with massive embolus with 60% or more of the pulmonary circulation compromised are critically ill. Right heart failure may progress to cardiovascular collapse with hypotension, coma, and death.

Sub-massive Pulmonary Embolus
A symptomatic pulmonary embolus presents with tachycardia and tachypnea. There are signs of a pulmonary infarction with consolidation, rales, hemoptysis, pleuritic chest pain, pleural friction rub, pleural effusion, and fever. It is unusual to find all of the findings in a single patient and findings may be non-specific, such as malaise and fever.
Ventilation-Perfusion Scan
A normal perfusion scan exclude PE but is found in a minority. Perfusion defects are non-specific; about 1/3 of those with defects actually have a PE. The probability of a perfusion defect in a PE increases with the size, shape, and number of defects as well as the presence of normal ventilation scan. Mismatched perfusion defects (normal ventilation scan) which are segmental in size or larger are “high probability” defects; these are associated with a prevalence of PE ~ 80%. Three or more mismatched defects is associated with prevalence of ~ 90%. If there is a positive VQ scan and high clinical suspicion then the patient should be treated.

Spiral CT
This is a quick CT scan where the entire thorax is scanned in one breath-hold. Sensitivity is 64-93%; Specificity is 89-100% - best when embolism is large and poor when clots are smaller. Actually visualizes the clot and can diagnose other conditions. Cheaper than other tests.

6.3.4 Treatment of Venous Thromboembolism
Once diagnosis is established and particularly if symptomatic, patient should receive anticoagulation for 3 – 6 months.

Prophylaxis Post-Stroke
- Age – over the age of 40 moderate risk.
- Over the age of 60 even with minor surgery at high risk.
- Highest risk:
  - major surgery
  - hip and knee fractures
  - major trauma
  - SCI
  - hemiplegic stroke

Heparin Therapy
Heparin has been shown to reduce the risk of DVT and PE in acute stroke survivors. Anticoagulation strategies include unfractionated heparin (UFH), low molecular weight heparin (LMW), and heparin analogues.

Advantages and Disadvantages of Heparin Use

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acts immediately</td>
<td>Poor subcutaneous bioavailability when given in low doses</td>
</tr>
<tr>
<td>Proven Efficacy in high risk patients</td>
<td>Short half-life</td>
</tr>
<tr>
<td>Can be neutralized</td>
<td>Risk of thrombocytopenia (minimal with prophylaxis)</td>
</tr>
<tr>
<td>Reference drug</td>
<td>Risk of bleeding (minimal)</td>
</tr>
<tr>
<td></td>
<td>Not sufficiently effective in very high risk groups</td>
</tr>
</tbody>
</table>
**Unfractionated Heparin**

Heparin is very individual specific. Heparin inactivates thrombin and anti-thrombin (non-specific in its action).

**Unfractionated Heparin in Acute Stroke Patients**

In 2 RCTs of acute stroke patients, low-dose unfractionated heparin (5000 units s/c q8h) reduced the rate of DVT from 73-75% in the placebo group to 13-22% in the treatment group.

**Unfractionated Heparin in SubAcute Stroke Patients**

There are no studies of prophylaxis in rehab stroke patients. Accepted use is to maintain while at high risk (i.e., bedridden, in a wheelchair, paralysis). There is no accepted stop date with a trend to longer and more frequent use.

**Low Molecular Weight (LMW) Heparin**

LMW heparin has a quantifiable and predictable anticoagulant effect. It doesn’t inactivate thrombin but does inactivate anti-thrombin. Drugs include:

- Dalteparin (Fragmin) 5000 units OD.
- Tinzaparin (Innohep) weight adjusted or 4500 units OD.
- Enoxaprin (Lovenox) 30 mg BID or 40 mg OD.

LMW heparin is easy to administer. There is no need to monitor. Patients appear to prefer it when monitoring is required. LMW heparin is standard treatment in high-risk patients:

- orthopedic surgery
- high risk medical patient
- DVT or pulmonary embolus

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**Forest Plot of the Effectiveness of Heparin or LMW Heparin in Preventing DVT Following Stroke**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>Weight %</th>
<th>DR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin vs Placebo</td>
<td>2/16</td>
<td>12/16</td>
<td>2.17 (0.05, 0.31)</td>
<td>32.64</td>
<td>0.11 (0.05, 0.19)</td>
</tr>
<tr>
<td>Subtotal (55%)</td>
<td>35</td>
<td>177</td>
<td>33.61</td>
<td>0.10 (0.06, 0.17)</td>
<td></td>
</tr>
<tr>
<td>Unfractionated Heparin vs Placebo</td>
<td>12/16</td>
<td>117/161</td>
<td>0.79 (0.70, 0.90)</td>
<td>34 (Treatment), 120 (Control)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Q: 1.01, df = 1 (P = 0.31), I² = 0%</td>
<td>Test for overall effect: Z: 6.86 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Molecular Weight Heparin</td>
<td>5/255</td>
<td>1/165</td>
<td>6.89 (0.07, 4.74)</td>
<td>17.29</td>
<td>0.29 (0.09, 0.59)</td>
</tr>
<tr>
<td>Test for heterogeneity: Q: 1.88, df = 1 (P = 0.37), I² = 0%</td>
<td>Test for overall effect: Z: 6.86 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95%)</td>
<td>1111</td>
<td>1025</td>
<td>100.00</td>
<td>0.22 (0.09, 0.55)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Q: 7.65, df = 6 (P = 0.0990), I² = 73.7%</td>
<td>Test for overall effect: Z: 3.18 (P = 0.0015)</td>
<td></td>
<td></td>
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</tbody>
</table>

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**Unfractionated Heparin**

Heparin is very individual specific. Heparin inactivates thrombin and anti-thrombin (non-specific in its action).

**Unfractionated Heparin in Acute Stroke Patients**

In 2 RCTs of acute stroke patients, low-dose unfractionated heparin (5000 units s/c q8h) reduced the rate of DVT from 73-75% in the placebo group to 13-22% in the treatment group.

**Unfractionated Heparin in SubAcute Stroke Patients**

There are no studies of prophylaxis in rehab stroke patients. Accepted use is to maintain while at high risk (i.e., bedridden, in a wheelchair, paralysis). There is no accepted stop date with a trend to longer and more frequent use.

**Low Molecular Weight (LMW) Heparin**

LMW heparin has a quantifiable and predictable anticoagulant effect. It doesn’t inactivate thrombin but does inactivate anti-thrombin. Drugs include:

- Dalteparin (Fragmin) 5000 units OD.
- Tinzaparin (Innohep) weight adjusted or 4500 units OD.
- Enoxaprin (Lovenox) 30 mg BID or 40 mg OD.

LMW heparin is easy to administer. There is no need to monitor. Patients appear to prefer it when monitoring is required. LMW heparin is standard treatment in high-risk patients:

- orthopedic surgery
- high risk medical patient
- DVT or pulmonary embolus

---

**Forest Plot of the Effectiveness of Heparin or LMW Heparin in Preventing DVT Following Stroke**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>Weight %</th>
<th>DR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin vs Placebo</td>
<td>2/16</td>
<td>12/16</td>
<td>2.17 (0.05, 0.31)</td>
<td>32.64</td>
<td>0.11 (0.05, 0.19)</td>
</tr>
<tr>
<td>Subtotal (55%)</td>
<td>35</td>
<td>177</td>
<td>33.61</td>
<td>0.10 (0.06, 0.17)</td>
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</tr>
<tr>
<td>Unfractionated Heparin vs Placebo</td>
<td>12/16</td>
<td>117/161</td>
<td>0.79 (0.70, 0.90)</td>
<td>34 (Treatment), 120 (Control)</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Q: 1.01, df = 1 (P = 0.31), I² = 0%</td>
<td>Test for overall effect: Z: 6.86 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Molecular Weight Heparin</td>
<td>5/255</td>
<td>1/165</td>
<td>6.89 (0.07, 4.74)</td>
<td>17.29</td>
<td>0.29 (0.09, 0.59)</td>
</tr>
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</tbody>
</table>
LMW Heparin in Acute Stroke Patients

LMW vs UF Heparin in Acute Stroke Patients
There are 5 RCTs (Turpie et al. 1992; Dumas et al. 1994; Hillbom et al. 2002; Diener et al. 2006; Sherman et al. 2007) comparing LMW to UF Heparin in acute stroke patients. 3 of the RCTs were positive (Turpie et al. 1992; Hillbom et al. 2002; Sherman et al. 2007) and 2 RCTs showed no significant difference (Dumas et al. 1994; Diener et al. 2006). Meta-analysis of 1900 acute stroke patients found significant difference (23 DVT in treatment group and 45 in placebo group, p=0.04) (Sandercock et al. 2008). There is an associated dose-dependent risk of intra- and extra-cranial hemorrhage with UFH. There is strong evidence that low molecular weight heparin is more effective with less risk of hemorrhagic complications than unfractionated heparin. Warfarin is an effective anticoagulant but is less reliable, more cumbersome to use and has more bleeding complications than LMW heparin when it comes to prophylaxis.

LMW vs UFH Heparin

<table>
<thead>
<tr>
<th>Authors</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie et al. (1992)</td>
<td>87 stroke patients randomized within 7 days to Orgaran or UFH s/c bid x max 14 days. DVT incidence 9% in LMWH and 31% in UFH.</td>
</tr>
<tr>
<td>Dumas et al. 1994</td>
<td>179 stroke patients randomized within 3 days to Orgaran OD or UFH BID for minimum of 9 days. No significant difference in DVT incidence.</td>
</tr>
<tr>
<td>Hillbom et al. 2002</td>
<td>212 stroke patients randomized within 2 days to either enoxaparin or UFH for 10 days. Over 3 months incidence of DVT or PE was 19.7% in LMWH and 34.7% in UFH (p=0.044).</td>
</tr>
<tr>
<td>Diener et al. 2006</td>
<td>545 acute stroke patients received 3000 units certoparin OD or 5000 UFH TID x 12-16 days. During Rx period 17 LMWH and 24 UFH patients developed DVT (p=0.29).</td>
</tr>
<tr>
<td>Sherman et al. 2007</td>
<td>1,762 acute stroke patients non-ambulatory randomized 40 mg enoxaparin OD or 5,000 units UFH BID x 10 days. Symptomatic DVT 1 in LMWH vs 4 in UFH (p=0.18). Asymptomatic DVTs 66 vs 114 (p&lt;0.0001).</td>
</tr>
</tbody>
</table>

**HIGHLIGHTED STUDY**

**Methods:** 5 RCTs of LMW Heparin vs. UF Heparin (n=705).

**Results:** DVT in 13% of LMWH and 22% of UFH. Odds ratio 0.52 (CI 0.56-0.79). More important outcomes of death and intracranial hemorrhage were small and no significant differences.

**HIGHLIGHTED STUDY**
Methods: The Acute DVT Study was a randomized, open-label study that compared the efficacy and safety of rivaroxaban with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients with acute, symptomatic DVT. The Continued Treatment Study (EINSTEIN–Extension) was a double-blind study in which patients with confirmed symptomatic DVT or pulmonary embolism who had been treated for 6 or 12 months with a vitamin K antagonist or rivaroxaban were randomly assigned to receive continued treatment with rivaroxaban or placebo. For both studies, the primary efficacy outcome was symptomatic, recurrent venous thromboembolism.

Results: The principal safety outcome — first major or clinically relevant nonmajor bleeding — occurred in 139 patients (8.1%) given rivaroxaban and in 138 patients (8.1%) given standard therapy (hazard ratio with rivaroxaban, 0.97; 95% CI, 0.76 to 1.22; P=0.77). Rivaroxaban alone is as effective as standard therapy, with similar safety, for the treatment of acute DVT and that when treatment is continued, rivaroxaban is very effective in preventing recurrences, as compared with placebo, and has an acceptable risk of bleeding.

HIGHLIGHTED STUDY


Methods: The EINSTEIN–PE study was a randomized, open-label trial of the efficacy and safety of rivaroxaban as compared with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was clinically relevant bleeding, which was defined as a composite of major or clinically relevant nonmajor bleeding.

Results: Recurrent nonfatal venous thromboembolism was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard-therapy group. The primary efficacy outcome occurred in 50 patients (2.1%) in the rivaroxaban group as compared with 44 patients (1.8%) in the standard-therapy group, for a hazard ratio of 1.12 (95% confidence interval [CI], 0.75 to 1.68; P=0.003 for a one-sided noninferiority margin of 2.0 and P=0.57 for superiority). By day 21, at the end of twice-daily rivaroxaban administration, the primary efficacy outcome had occurred in 18 patients (0.7%) in the rivaroxaban group and in 21 patients (0.9%) in the standard-therapy group. Oral rivaroxaban alone provided protection from recurrent venous thromboembolism that was similar to the protection provided by standard therapy, with similar bleeding rates. During a mean study duration of approximately 9 months, there was a recurrence in 2.1% of patients in the rivaroxaban group and 1.8% of those in the standard-therapy group. The primary safety outcome of major or clinically relevant nonmajor bleeding was observed in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group, and major bleeding was observed in 1.1% and 2.2% of patients, respectively.

HIGHLIGHTED STUDY


Methods: In the RE-COVER study, a double-blind, double-dummy, randomized trial, six months of treatment with dabigatran, at a fixed dose of 150 mg twice daily, was compared to dose-adjusted warfarin therapy, after initial parenteral anticoagulation.

Results: It was shown that dabigatran is noninferior to warfarin (when warfarin is dose-adjusted to achieve and maintain an INR in the range of 2.0 to 3.0) in the prevention of recurrent events. Venous thromboembolism or related deaths occurred in 30 patients in the dabigatran group as compared with 27 patients in the warfarin group. The rates of bleeding with dabigatran were similar to or lower than those with warfarin. There were 20 major bleeding events in the dabigatran group as compared with 24 in the warfarin group, and there were fewer episodes of nonmajor bleeding with dabigatran than with warfarin.
Warfarin
An International Normalized Ratio (INR) of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism while minimizing the risk of haemorrhage associated with higher INRs. Anticoagulation effect of warfarin is accomplished by inhibiting vitamin K epoxide reductase. Initially there is a greater decrease in levels of protein C and protein S than the vitamin K dependent factors II, VII, IX, X. This disproportionate decrease in coagulation factors increases the risk of developing a clot in the first 5 days after warfarin initiation. Concomitant use of heparin is usually required during the transition in therapy.

Advantages and Disadvantages of Warfarin Use

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral administration</td>
<td>Risk of bleeding</td>
</tr>
<tr>
<td>Proven Efficacy</td>
<td>Delayed onset of action</td>
</tr>
<tr>
<td></td>
<td>Delayed neutralizing</td>
</tr>
<tr>
<td></td>
<td>Frequent monitoring necessary</td>
</tr>
<tr>
<td></td>
<td>Many drug interactions</td>
</tr>
</tbody>
</table>

Mechanical Treatments
Compression stockings have not been shown to reduce the incidence of DVTs post stroke.

HIGHLIGHTED STUDY

Methods: 98 acute stroke patients Rx with standard treatment (control) or standard treatment and compression stockings.
Results: There were no significant difference between the groups.

HIGHLIGHTED STUDY

Methods: 2,518 patients admitted to hospital (64 sites) within 1 week of stroke and immobile randomized to routine care +/- graduated compression stockings.
Results: No significant difference between the groups.

HIGHLIGHTED STUDY
Methods: 3,114 acute immobile stroke patients from 112 centres randomized to wear thigh-length or below-knee stockings.
Results: Incidence of proximal DVT within 30 days was significantly higher in below-knee stocking group compared with above-knee group (8.8% vs. 6.3%, p=0.008).

HIGHLIGHTED STUDY
CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomized controlled trial.

Methods: 2876 acute immobile stroke patients from 94 centres randomized to receive intermittent pneumatic compression (IPC) or not within 3 days of stroke; IPC was worn at all times for a minimum of 30 days or until second screening. Compression Doppler ultrasound (CDU) of both legs performed at 7-10 days, 25-30 days or when symptomatic of DVT. 3,114 acute immobile stroke patients from 112 centres randomized to wear thigh-length or below-knee stockings.
Results: Incidence of proximal DVT within 30 days was significantly higher in non-IPC group compared with IPC group (12.1% vs. 8.5%, p=0.001); adjusted OR was 0.65 (95% CI 0.51-0.84). There were significantly more skin breaks in the IPC group.

Conclusions Re Prevention of Deep Venous Thromboembolism
There is strong evidence that anticoagulation significantly reduces incidence of DVT when compared to placebo. There is strong evidence that LMW heparin is better than UF heparin for reducing the risk of hemorrhagic complications and decreasing the frequency of venous thromboembolism. There is strong evidence that graduated compression stockings do not reduce the risk of DVT. There is strong evidence that thigh length compression stockings reduce the risk of DVT when compared to below knee stockings. There is strong evidence that intermittent pneumatic compression (IPC) reduces the risk of DVT when compared to no treatment with IPC. There is moderate evidence heparin equivalent to both pneumatic compression and electrical stimulation in reducing risk of DVTs.

Conclusions Re DVT in Stroke
Almost all literature on stroke deals with the early phase of the stroke. Prophylaxis decreases the risk of DVT post stroke. Fatal PE may account for 25% of acute CVA – associated deaths. Risk of hemorrhagic transformation of stroke is low. Risk declines in chronic phase. Paralyzed, bedridden, or wheelchair-bound patients should be anticoagulated. LMW Heparin is now the route to go. There is no evidence supporting the use of graded compression stockings or pneumatic compression.

6.4 Post-Stroke Seizures

6.4.1 Introduction
Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires more than one seizure. One seizure in association with an enduring disturbance of the brain is capable of giving rise to other seizures has been defined as epilepsy (Fisher et al. 2005). Post stroke seizures may occur soon after stroke or be delayed; each appears to be
associated with differing pathogeneses. Most seizures are single, either partial or generalized (Ferro and Pinto 2004). Wiebe and Butler (1998) noted that, “Seizures are the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex.” Younger patients and men are at increased risk for seizure activity post stroke (Arboix et al. 1997; Giroud et al. 1994). A lesion involving the cerebral cortex is a prerequisite for the development of epilepsy (Skyhoj Olsen et al. 1987).

6.4.2 Incidence of Post Stroke Seizures

Wiebe and Butler (1998) observed that the incidence of seizures following ischemic or hemorrhagic stroke in earlier series is noted to be highly variable ranging from a low of 7.7% to a high of 42.8%. In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). The average risk of seizures is 10% within 9-10 years after stroke and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burr et al. 1997). At least two studies suggest a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo 1992; Paolucci et al. 1997). Seizures usually occur during the first 1 to 2 weeks following stroke. Hemorrhagic stroke patients have been found to have an almost 2-fold risk of developing a seizure following stroke compared to patients with an ischemic lesion (Bladin et al. 2000).

HIGHLIGHTED STUDY

Methods: Clinical data prospectively collected on 827 patients with completed stroke.
Results: 10% of patients had seizures during their first admission during 2 to 5 years follow-up. Seizures occurred only in those patients with hemispheric lesions. 39% of seizures occurred by the first day, 57% occurred by the first week and 88% occurred by the first year.
6.4.3 Types and Timing of Post-Stroke Seizures

Black et al. (1983) reported that 39% of seizures occurred within the first 24 hours, 57% within the first week and 88% within the first year. The overall percentage after stroke of focal seizures was 50%, generalized seizures 32%, focal seizures with secondary generalization 15%, and complex partial seizures 2.5% (Wiebe-Velazquez, Blume 1993).

6.4.4 Impact of Seizures on Outcomes

Whether seizures worsen outcomes remains unclear. Vernino et al. (2003) reported new-onset seizure among patients with ischemic stroke to be an independent risk factor for mortality on multivariate analysis (Relative risk 1.81; 95%CI 1.16-2.83). Bladin et al. (2000) also reported higher mortality among patients with seizures at 30 days and 1 year, compared to patients who were seizure free (25% vs. 7% and 38% vs. 16%). However, the authors did not control for the confounding effects of stroke severity or comorbidity. The results of other studies have not supported an increased risk of mortality (Labovitz et al. 2001; Reith et al. 1997).

6.4.4 Treatment of Post-Stroke Seizures

There is no evidence that prophylactic anticonvulsive treatment is beneficial post stroke. There is consensus opinion that post-stroke seizures should be treated with anticonvulsant medication to prevent seizure recurrence. Standard first-line therapy usually includes carbamazepine, valproic acid and phenytoin. Phenytoin is known to interact with warfarin. Newer anti-epileptic drugs such as lamotrigine may be better tolerated and have a better side-effect profile than some of the older drugs. There is some concern that anti-epileptic drugs may impair recovery post stroke. Benzodiazepines as an ongoing treatment should be avoided due to its sedating effects unless seizure activity is uncontrolled.

Treatment of Status Epilepticus Post Stroke

Benzodiazepines are considered the best first-line drugs for managing status acutely with a seizure control rate of approximately 79%. Both Lorazepam and Diazepan given intravenously are acute treatment strategies, although Lorazepam may be more effective in terminating status epilepticus (59-89% vs. 43-76%) and has longer lasting anticonvulsant properties (12 hours vs. 20 Minutes for Diazepam). Midazolam 10 mg given by the buccal and intranasal route is an alternative where intravenous medications are difficult to give.

6.4.5 Driving and Post-Stroke Seizures

The patient should be assessed by a neurologist and an EEG performed. The patient will need to be seizure-free for at least 6 months, on stable treatment and assessed by a neurologist conducting the EEG before they can drive again. Individual circumstances may warrant prolonging or reducing the time period suggested.
6.5 Thalamic/Central Pain States Post Stroke (CPSP)

CPSP is a syndrome characterized by sensory disturbances and neuropathic pain. In 40-60% of CPSP patients, the onset of central pain occurs more than one month following the stroke. The incidence of CPSP has been reported as high as 8% but is generally felt to be much lower. According to the best studies, central post-stroke pain occurs in less than 2% of stroke patients.

6.5.1 Pathophysiology of CPSP

CPSP is often referred to as “thalamic pain”. CPSP can occur post lower brainstem, thalamic and even suprathalamic strokes. CPSP is associated with lesions involving the spino-thalamic pathway with disturbance in temperature and pain sensation. The pathophysiology of CPSP remains unknown. Although it requires damage to spino-thalamic pathway; however, not all damage to the STP leads to CPSP. All patients with CPSP have impaired sensation to temperature (hot, cold) and pain (pinprick) which is indicative of damage to the spinothalamic tract. Touch, 2-point discrimination and vibration sense remain intact; CPSP is therefore not mediated by the lemniscal pathway.

Post-stroke, most cases develop at 1-2 months although some develop it at 1-6 years. Often there is a delay in the onset of symptoms after the onset of stroke. One potential mechanism is the subthreshold activation of nociceptive neurons in which nociceptive neurons discharge in response to a normally non painful stimulus. Most commonly CPSP involves lesions within the ventrocaudal nuclei of the thalamus, particularly within ventroposterior inferior nucleus. Cutaneous nociceptive input is encoded and conducted via specific neurons in ventromedial thalamus. Release of inhibition may produce the CPSP. Most cases of CPSP are associated with hyperalgesia +/or allodynia. Paradoxical sensory deficit and hyperalgesia suggests central sensitization of 3rd and 4th order CNS neurons as a result of loss of spino-thalamic or thalamo-cortical input.
6.5.2 Clinical Symptoms of CPSP

CPSP is described as a “burning” sensation in association with parasthesiae (tingling, pins & needles, numbness). It is often described as ripping, tearing, pressing, twisting, aching, pricking and lacerating pain. Leijon and Boivie (1989) in their study of 23 CPSP patients noted little difference in pain character in relation to the stroke site. “Burning” pain was more commonly described with brainstem lesions while lacerating pain was more often with suprathalamic strokes. Pain normally occurs within an area smaller than the area of sensory impairment. Generally it is described as constant pain and often associated with spontaneous paroxysms of pain; can be exacerbated by physical movement, emotional stress, loud noises or voices, changes in weather, cold and light touch. Virtually all cases of CPSD report spontaneous or evoked parasthesias +/- dysaesthesia.

*Dysesthesia*: Unpleasant sensations, either spontaneous or evoked (Andersen et al. 1995).

*Allodynia*: Abnormally unpleasant somatosensory experience, often poorly localized, elucidated by normally non-nociceptive stimuli (Andersen et al. 1995).


6.5.3 Treatment of CPSP

CPSP has been generally regarded as intractable to treatment. It is typically treated with pharmacological interventions – tricyclic antidepressants and anticonvulsants combined with opioid analgesics has been usual management. Treatment has been generally unsatisfactory.

*Amitriptyline*

There is conflicting evidence (based on 2 RCTs) amitriptyline reduces pain post-stroke (Leijon and Boivie 1989; Lampl et al. 2002).

---

**HIGHLIGHTED STUDY**


**Methods**: Double-blind, 3 phase crossover placebo controlled trial of 15 patients. Treatment given in randomized order, for 4 weeks, separated by 1 week washout periods where patients administered amitriptyline, carbamazepine and placebo.

**Results**: Amitriptyline produced significantly greater reduction of pain when compared to placebo at week 4.

---

**HIGHLIGHTED STUDY**


**Methods**: 39 CPSP patients randomly receive amitriptyline (n=20) or placebo (n=19) over 1 year.

**Results**: No differences in occurrence, intensity, type, site or distribution of pain between 2 groups.
Naloxone
There is moderate evidence (1 RCT) naloxone does not reduce central post-stroke pain (Bainton et al. 1992).

**HIGHLIGHTED STUDY**

**Methods:** 20 CPSP patients received naloxone (up to 8 mg) vs. normal saline in randomized cross-over trial. VAS and verbal pain scores obtained before and after injection with 2-3 week washout period.

**Results:** No immediate or long-term differences in pain relief between 2 groups.

I.V. Lidocaine
There is moderate evidence (1 RCT) lidocaine results in short-term (45 min) pain relief only (Attal et al. 2000).

**HIGHLIGHTED STUDY**

**Methods:** 16 patients (6 with stroke) received both lidocaine vs. saline intravenous injections 3 weeks apart in a randomized cross-over trial. Patients recorded pain using VAS.

**Results:** Lidocaine significantly better than saline in reducing intensity of spontaneous ongoing pain for up to 45 minutes post injection; no difference at 6 hours post injection.

Anticonvulsants
There is moderate evidence (1 RCT) Lamotrigine alternative to TCAs in CPSP treatment (Vestergaard et al. 2001).

**HIGHLIGHTED STUDY**

**Methods:** 30 CPSP patients in double-blind, placebo-controlled cross-over study of lamotrigine – two 8-week Rx periods separated by 2 weeks of washout.

**Results:** Lamotrigine 200mg/day reduced median pain score to 5, vs. 7 for placebo (p=0.01); no effect for lower doses. 44% of CPSP patients responded to treatment.

Narcotics
There is moderate evidence (1 RCT) high strength u-opioid agonist levorphanol reduces CPSP. There is moderate evidence (1 RCT) I.V. morphine results in analgesia; only a minority may benefit from long-term treatment (Attal et al. 2002).

**Methods:** Morphine infusion (9-30mg) assessed in double-blind, placebo-controlled crossover study of 15 patients (6 CPSP + 9 SCI pain).

**Results:** Morphine significantly reduced intensity of brush-induced allodynia only; no change in VAS overall. However, 7 (46%) responded to morphine. All were put on oral morphine after study; only 3 (20%) were taking morphine at one year.

**Mexiletine**

There is limited evidence Mexiletine reduces CPSP (Awerbuch et al. 1990).

**HIGHLIGHTED STUDY**


**Methods:** 9 patients (8 with stroke) given 150mg mexiletine x 3 days followed by 300mg/day for 3 days and then 10mg/kg/day x 1 month.

**Results:** Significant improvement in pain in 8 of 9 patients.

**Motor Cortex Stimulation**

There is limited evidence that brain stimulation reduces CPSP (motor cortical stimulation> deep brain stimulation > spinal cord stimulation) (Katayama et al. 1998; 2002).

**HIGHLIGHTED STUDY**


**Methods:** 31 CPSP patients treated with motor cortex stimulation through surgically implanted devices delivering a pulse of 0.2 msec duration, frequency of 25-50 Hz and intensity of 2-8V; Stimulation applied 10-20 min for each time.

**Results:** Satisfactory pain control was achieved in 74% (23) during first one-week period.

**Fluvoxamine**

There is limited evidence SSRI fluvoxamine is useful in CPSP relatively early after stroke onset (Shimodozono et al. 2002).
HIGHLIGHTED STUDY

Methods: 28 patients with CPSP received SSRI fluvoxamine 50 mg/day. Doses increased or maintained (max 125 mg/day) depending on symptoms for 2-4 weeks.

Results: Patients mean VAS and Zung’s Self-rating Depression Scale decreased (p<0.01). Subset analysis showed in stroke < 1 year, VAS decreased (p<0.001); > 1 year no change in VAS.

Algorithmic Treatment Approach to Central Post Stroke Pain
The majority of patients suffering from CPSP are intractable to therapeutic interventions. First line treatments include tricyclic antidepressants and antiepileptics. Second line treatment is opioids. Second-line treatment would include stronger narcotic analgesics such as Oxycodone (short-acting or long-acting) or Morphine (long-acting). Alternative anti-epileptics such as Dilantin, Gabapentin and Pregablin.
References


