Venous Thromboembolism in a Patient Population Treated with Electroconvulsive Therapy

Dr Steve Prowacki
RANZCP SEN Conference
18th August 2018
Summary

• Cases suggesting a trend to ↑ rates of VTE in our ECT Service
• Discuss cases and risk factors
• Review the limited literature
• Lack of clear causality
• Prophylaxis options
• Propose sparse prevention algorithm
• Invite discussion and collaboration with others
Introduction

• Increased frequency of VTE events observed in our ECT Service over time
  – ? age related
• Psychiatric patients have mortality rates 2-3 times higher than general population

WHY?

• Multiple probabilities which include many risk factors
• VTE prophylaxis prominent in orthopaedic inpatient procedural practice and more recently in medical inpatient practise – but not psychiatry
• Little interest in psychiatry, patients excluded from large studies
• ECT patients have characteristics of both at risk surgical and medical patients
ECT Opposed Administratively & Socially

• Recent experience in Qld MHRT
• ECT is astoundingly safe with low mortality and morbidity with a marked clinical effect on suicide and suicidality
• No in-theatre deaths in >100,000 ECTs in our service
• Are we getting the message out to the public about the illness level and associated risks vs the treatment risks and benefits (ie. low level of risk & high comparative efficacy)
A Brisbane hospital accused of impairing a patient's memory after more than 140 electric shock treatments has been taken to court.

Mental health examinations filed along with the application revealed the man, held under an involuntary treatment order, claimed the treatments affected his memory and “harms his brain”.

An expert brought in by Public Advocate Mary Burgess to examine him agreed there was “clear evidence of short-term memory impairment”.

Attempts to reduce the weekly treatments in August were said to result in a “rapid decline in mental state”.

He was charged with property offences in August 2011 after he threw chairs in the food court of the Royal Brisbane and Women’s Hospital and damaged a car mirror, fire panel control box and glass door window.

A spokeswoman for Metro North Hospital and Health Service, the hospital’s governing body, said modern ECT was safe and effective at treating severe depression, bipolar disorder and schizophrenia.

“Decisions to use ECT are always made very carefully in accordance with the law by a team of highly qualified clinical staff, based on a thorough assessment of the patient’s clinical condition and the goal of delivering the best outcomes,” she said, in a statement.
Belmont Total Annual ECT Procedures 2010 - 2017 (27,149 Total Treatments)

Number of Patients

Year of Treatment


2626 2866 3058 3738 3847 3699 3533 3782
Risk

• Observed increase in cases over time
• Is this related to ECT changes such as anaesthesia, pressor effects, assertive fasting, vein irritation, patients remaining more sedated after ECT, long lists?
• “Psych-out” bias (Seshia, Makhinson & Young, 2015) - there is a tendency to attribute symptoms in psychiatric patients to mental illness, a framing bias
• Comments even by psychiatric professors
Psych-out
Evolution of observed problems in our service

1. Cardiolipin pathology associated ECT in an 18yo woman – Warfarin Rx (result – safe outcome)
2. Epilepsy and stupor in a 57yo woman with prolonged psychomotor impairment with a fatal outcome after 6 weeks bed ridden in a medical ward
3. Maintenance ECT in a 77yo man, pre-procedure detection of large saddle embolus, VTE prophylaxis had been ceased by physician 3 months after a bladder bleed while on enoxaparin
4. Post-Maintenance ECT associated collapse, pulmonary embolus – day after ECT in a young woman 37yo (fatal)
5. Course ECT associated PE in a 67yo male, DVT 3 months previously, GP ceased Xarelto at admission – multiple pulmonary emboli after ECT number 4
6. Course ECT – Cephalic vein thrombosis associated with factor V Leiden Disease diagnosed – saline flush no cuffing
7. Maintenance ECT associated deep vein thrombosis at arm cannula site, no association found, no cuffing, saline flush ± drip
Venous Thromboembolism (VTE)

• Causes up to 7% of inpatient deaths (ACSQHC, 2014)
• Up to 2.2% of psychiatric inpatients have VTE/DVT (Heraudeau et al., 2012)
• Surgical VTE prophylaxis is used as a quality indicator but not in medical patients (AIHW, Sept 2009)
Literature Review

• Observational evidence from which psychiatric patients are mainly excluded (eg. IMPROVE)

• Takeshima, 2018, a study of 2,468 psychiatric inpatients over 8 years
  – 2.3% of patients had VTE
  – 4% of inpatient deaths associated with PE
  – Highest with catatonia (61.1%); 4.1% of restrained pts; PE in 76.9% of VTE pts; 97.4% of VTE pts were asymptomatic
  – Contrast enhanced CTPA important in diagnosis
Increased Risk of Thrombosis and Antipsychotic Agents

- Hospitalization
- Immobilization
- Use of antipsychotic/antidepressant agents
- All appear to be independent risk factors for thrombosis
- Psychosis may independently activate phospholipid system

(Masopust et al., 2011)
Increased Risk in Psychiatric Patients

- Long term hospitalizations
- Immobilization (restraint or psychomotor retardation)
- Catatonic stupor, Neuroleptic Malignant Syndrome
- Overall decreased mobility
- Dehydration
- Sedation
  - Specific neuroleptic effects on prolactin, metabolic effects
  - Decreased blood pressure
  - Antiphospholipid effects
- Diagnosis of schizophrenia and bipolar affective disorder

(Hem, Steen & Opjordsmoen, 2008)
(Stahl, Mignon & Meyer, 2009)
Takeshima, Ishikawa, Shimizu, Kanbayashi & Shimizu, 2018

- Incidence of venous thromboembolism in psychiatric inpatients at Akita - 2,468 patients in a 36 bed unit over 8 years
- 4% sudden unexpected deaths were PE associated
- Antipsychotic medications increased the risk
- 11.6% of physically restrained patients had DVT
- 25.3% catatonia patients had DVT
- Excluded continuation ECT or non-psychiatric medical hospitalization in psychiatric patients
- Used D-Dimer and found it the most useful single investigation
Pulmonary Embolus
Identifying Risk

- Not easy – 97.4% of pts asymptomatic (Takeshima et al., 2018), tends to be retrospective as prospective checking is often considered too expensive and too difficult
- Physician literature does not support routine testing for risk (the “Futility of Factor V Testing”)
- It is not simple – genetic, acquired, relates to age, diagnoses, immobility, injury, pregnancy and cancer
- Controversial – do benefits of prophylaxis outweigh risks (Patel, 2015)
High Risk Thrombophilia

- Anti-thrombin deficiency - 1.8% per year (95% CI 1.1-2.6%)
- Protein C deficiency - 1.5% per year (1.1-2.1%)
- Protein S deficiency - 1.9% per year (1.3-2.6%)

(Lijfering et al., 2009)
Moderate Risk Thrombophilia

- Factor V Leiden – 0.5% per year (0.4-0.6%)
- Prothrombin gene mutation – 0.3% per year (0.2-0.5%)
- Factor VIII – 0.5% per year (0.4-0.5%)

(Lijfering et al., 2009)
Low Risk Thrombophilia

- Factor IX – 0.1% per year (0.02-0.2%)
- Factor XI – 0.2% per year (0.06-0.6%)
- Hyperhomocysteinemia – 0.1% per year (0.05-0.3%)

(Lijfering et al., 2009)
Case No: 1

• 57 year old lady with Bipolar Disorder and Epilepsy prone to serious depression, responsive to ECT (3 episodes over 15 years)
• Found in a withdrawn psychomotor impaired state
• Referred to general hospital by Psychiatrist → ECT suggested → 6 weeks in medical ward → ECT commenced → fatal PE after ECT No: 2
Autopsy Pulmonary Thrombosis
Case No: 2

- 67 year old male hospital engineer with severe depression and OCD
- had DVT left calf and PE $\rightarrow$ Rx rivaroxaban
- Rx ceased by physician after 3 months
- Respiratory distress after ECT No: 4 (no prophylaxis)
- No further ECT with a poor mood outcome
Pulmonary Embolism CTPA
(Coronal)
Pulmonary Embolism CTPA
(Sagittal 1)
Pulmonary Embolism CTPA
(Sagittal 2)
77 year old male presented for day patient maintenance ECT:

- Stated he felt unwell, no specific symptoms
- Tachycardia
- Elevated blood pressure
- ECG Changes (S₃, Q₃, T₃)
- Physician had ceased DOAC 2 months previously, past history DVT
CTPXA Report

dxg/kam1

CT PULMONARY ANGIOGRAM

History: Assess for possible pulmonary embolus.

Findings: Contrast infusion spiral CT through the thorax.

There is a saddle embolus involving the pulmonary trunk extending into the right and left main pulmonary arteries with almost total occlusion of the right main pulmonary artery and significant narrowing of the left main and upper and lower lobe branches. There is no other mediastinal abnormality. There is no pulmonary nodule or mass. There are no areas of collapse or consolidation.

Summary: Positive study with major saddle embolus involving the pulmonary trunk extending into the right and left main pulmonary arteries.
Pulmonary Embolism CTPA
(Coronal 1)
Case No: 4

• A 36 year old female architect with a past history of severe depression on a schedule of MECT every 5 weeks, sends an image of her left arm
  – Superficial thrombosis (non cuffed arm)
  – Superficial and cephalic vein thrombosis
  – Factor V defect
  – Saline flushing with subsequent maintenance treatment
Cannulation Bruising & DVT
Cannulation Site 3 months later
Review of Patients

• 6 serious cases in about 4,000 treatments
• However when patients assertively checked >2% found to have VTE (Delluc et al., 2012)
• 1 mortality post ECT PE (next day, post ECT)
• Approximately 400 patients, suggest we miss detecting a few, perhaps many
Why There is a Risk

- Diagnoses that affect motility (psychomotor impairment)
- Diagnoses:
  - Factor V Leiden Disease
  - Cardiac disorders (arrhythmias)
  - Surgery/Medical
  - Other thrombophilia
    - Anti-thrombin deficiency
    - Factor VIII disease
    - Protein C deficiency
    - Protein S deficiency
    - Antiphospholipid disease
    - Sickle Cell Disease
    - Estrogen
Virchow’s Triad (1856)

- Stasis
- Vessel wall injury
- Hypercoagulability
Risk Factors for VTE Events

- **Genetic:**
  - FV Leiden Mutation
  - Protein C or S Deficiency
  - Anti-thrombin Deficiency
  - FII G 20210A mutation
  - Others include Factor VIII, high IX, high XI, reduced fibrinolysis

- **Acquired:**
  - Age >70
  - Malignancy
  - Antiphospholipid antibodies
  - Inflammatory Bowel Disease
  - Systemic Lupus Erythematosus
  - Nephrotic Syndrome
  - Obesity
  - Microalbuminuria

- **Environment:**
  - Infection
  - Surgery (Especially orthopaedic)
  - Trauma ?
  - Pregnancy
  - Oral contraception
  - Air travel

- **Uncertain:**
  - Smoking
  - High C reactive protein
  - High lipids
Gordon Parker: Melancholia
Calls for Risk Assessment in all Hospitalized Patients

- Risk assessment reduces the observed mortality to about 50%
- D-Dimer is useful for diagnosis if DVT occurs
- Risk assessment must balance clot risk vs bleeding risk
- Online risk assessment models (IMPROVE)
- **BUT** complex, time consuming models are not used; sparsely austere assessment often has good utility and is fast (see Gigerenzer who points to ST segment change as best ICU referral decision maker for cardiac)

(Raskob, 2016)
Preventive Interventions

• Many surgical VTE policies deem prophylaxis is to be used unless contraindicated (HITS, Von Willebrands, Haemophilia, low platelets following injury)

• Compression stockings

• Avoiding cuffing, legs or arms (ECT relevant)

• Mobilization encouragement

• Hydration

• Drug treatment, NIMC has reminders
Preventive Interventions (continued)

- **Heparin/Enoxaparin/Fraxiparine** – S/C injectables
- **Direct Oral AntiCoagulants (DOACs)**
- **Older agents** - Warfarin (difficult; laboratory monitoring required, Vitamin K reversible)
- **Oral agents** - 5 directly acting oral anticoagulants since 2008, including:
  - Apixaban
  - Rivaroxaban
  - Dabigatran

Reversal difficult
3 drugs in development

(Holbrook et al., 2016)
**Adult Venous Thromboembolism Risk Assessment Tool**

**1. Assess Venous Thromboembolism (VTE) Risk and Allocate Patient into Risk Category**

- **Higher Risk**
  - Total hip replacement, total knee replacement, or hip fracture surgery
  - Abdominal or pelvic surgery for cancer
  - Multiple major trauma
  - Acute spinal cord injury with paraplegia

- **Moderate Risk**
  - Patients who are not in either the lower- or higher-risk group

- **Lower Risk**
  - Ambulatory patient without VTE risk factors
  - Ambulatory patient with VTE risk factors but expected length of stay < 2 days
  - Minor surgery in patient without VTE risk factors

**2. Identify Contraindications and Other Conditions to Consider with Pharmacological Prophylaxis**

- **Absolute Contraindications**
  - Active haemorrhage
  - Severe trauma to head or spinal cord, with haemorrhage in last 4 weeks
  - Thrombocytopenia (platelets < 50 x 10^9/L) or coagulopathy
  - End stage liver disease (INR > 1.5)
  - Therapeutic anticoagulation with medication (e.g. warfarin, dabigatran, rivaroxaban, apixaban)

- **Relative Contraindication**
  - Intracranial haemorrhage within last year
  - Cranial surgery within 2 weeks
  - Intercostal or peripheral vascular surgery
  - Gastrointestinal or genitourinary haemorrhage within 3 months
  - Active eustachian tract lesions/epiglottitis
  - Hyperensive emergency
  - Post-operative bleeding concerns
  - Use of antithrombotic (e.g. aspirin, clopidogrel, dipyridamole)
  - Inherited bleeding disorder
  - High falls risk

- **Other Conditions**
  - Heparin-sensitivity or history of heparin-induced thrombocytopenia (HIT)
  - Fracture/Removal of epidural catheter or spinal needle (lumbar puncture) (current or planned)
  - Creatinine clearance < 30 mL/min (see recommendations elsewhere)
  - Acute stroke (Seek further advice from stroke service)
  - Neurosurgery (Seek further advice from Neurosurgery Consultant)
  - Weight < 50kg or > 100kg (consider dosage adjustment as per local guidelines)

**3. Identify Contraindications to Mechanical Prophylaxis**

- **Skin Lesion**
- **Severe peripheral vascular disease**
- **Severe dermatitis**
- **Lower leg trauma**
- **Severe lower leg oedema**

- **Recent lower limb DVT (anti-embolic stockings may be used)**
- **Massive leg oedema/pulmonary oedema due to congestive cardiac failure**
- **Obesity where correct fitting of stockings cannot be achieved**

- **Peripheral neuropathy** (Intermittent pneumatic compression can be used)

**NO WRITING**
## Adult Venous Thromboembolism Risk Assessment Tool

**Facility:**

<table>
<thead>
<tr>
<th>FAMILY NAME</th>
<th>MHN</th>
<th>GENDER</th>
<th>D.O.B</th>
<th>M.O.</th>
<th>ADDRESS</th>
</tr>
</thead>
</table>

### 4. Prescribe Appropriate Prophylaxis

**Higher Risk**

- Select one pharmacological option:
  - Enoxaparin 40 mg subcutaneous daily
  - Enoxaparin 20 mg subcutaneous daily if Creatinine Clearance < 30 ml/min (or use Heparin: 5000 units subcutaneous 8-12 hourly)
  - Dalteparin 5000 units subcutaneous daily
  - Low molecular weight heparin (LMWH) in patients with contraindication

- OR, No pharmacological prophylaxis because of contraindication or not advised

- AND select one mechanical device:
  - Graduated compression stockings / anti-embolic stockings
  - Intermittent pneumatic compression
  - Foot impulse device
  - No mechanical prophylaxis because of contraindication

- PLUS
  - Early mobilisation
  - Patient education

**Moderate Risk**

- Select one pharmacological option:
  - Enoxaparin 40 mg subcutaneous daily if Creatinine Clearance < 30 ml/min (or use Heparin: 5000 units subcutaneous 8-12 hourly)
  - Dalteparin 5000 units subcutaneous daily
  - Heparin 5000 units subcutaneous 8-12 hourly

- OR, No pharmacological prophylaxis because of contraindication or not advised

- AND select one mechanical device for patients not prescribing pharmacological prophylaxis:
  - Graduated compression stockings / anti-embolic stockings
  - Intermittent pneumatic compression
  - Foot impulse device
  - No mechanical prophylaxis because of contraindication

- PLUS
  - Early mobilisation
  - Patient education

**Lower Risk**

- Prophylaxis not required
- Early mobilisation
- Patient education

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5. Other Considerations

- Insertion or removal of epidural catheter or spinal needle (lumbar puncture) should be carried out ≥ 4 hours before a prophylactic dose of LMWH and ≥ 10 hours after a previously administered dose. For other agents, please refer to the Product Information.

**Orthopaedic Surgery:** Alternative agents may include:

- Knee replacement: dalteparin, naxaroxan, fondaparinux, apixaban
- Hip fracture: fondaparinux, aspirin in combination with LMWH
- If there is hip and knee replacement surgery, LMWH is preferred over heparin

6. Consider Duration of Therapy

**Medical Patients:**
- Continue until acute medical condition is stable, patient is mobile or until hospital discharge

**Surgical Patients:**
- Total hip replacement/hip fracture surgery: continue for 28 to 35 days
- Total knee replacement: continue for up to 14 days
- Lower leg immobilisation due to injury: until fully mobile
- Major general surgery: continue for up to 1 week or until fully mobile

**KEY:**

- LMWH = low molecular weight heparin
- e.g. enoxaparin, dalteparin

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Date completed: \_\_/\_/\_ Name: \_\_\_\_\_\_\_ Signature: \_\_\_\_\_\_\_ Designation: \_\_\_\_\_\_\_

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RISK VS UNCERTAINTY

RISK:
How should we make decisions when all relevant alternatives, consequences, and probabilities are known for certain?

Neoclassical economics, behavioral economics

UNCERTAINTY:
How should we make decisions when not all alternatives, consequences, and probabilities are known?


(World Minds, 2011)
Sparse Model of VTE Prophylaxis for Psychiatry

- Psychomotor retardation (any cause) - 2 points
- Past VTE (any time) - 1 point
- Age >70 - 1 point
- Any other risk factor - 1 point
- If no contraindication, treat if 2 or more points
Venous Thromboembolism Prophylaxis

Do the benefits outweigh the risks?

- Little psychiatric evidence published
- Question whether mortality is reduced even with major surgery where risk of major bleeding is increased
- 2.2% of identified thromboses after only 10 days admission to a psychiatric hospital (Delluc et al., 2012)
- Should it be mechanical, or pharmacological (LMWH, ORAL)
- Controversy 3 prevention vs 4 bleeds per 1000 (but hospitalized stroke patients) (Lederle, Zylla, MacDonald & Wilt, 2011)
- No cost benefit analysis in psychiatry

(Patel, 2015)
Conclusions

• VTE risk is present and likely increasing
• We may be causing some of it
• Prophylaxis is available— but is 3/28 enough?
• How to do it? Physicians helpful — ask re VTE prevention
• ? Safety of some of seizure improving interventions, ? K unintended consequence
• Discussion and work needed
References

- Australian Commission on Safety and Quality in Health Care., 2014
- Australian Institute of Health & Welfare., Sept 2009
- Croxford et al., 2015 (10.1136/bmjopen-2016-013263) [SEE HOLBROOK REF]
Contact Details
Email: steve.prowacki@healthecare.com.au