Endovascular Treatment for Acute Ischaemic Stroke due to Large-vessel Occlusion: Single-centre Experience

DCW Tang1, CY Chu1, R Li2, SWH Cheng2, RYT Ng3, JCH Tse1, AYT Lai1, THT Sung1, KYK Tang1, WKW Leung1, JLS Khoo1

1Department of Radiology, 2Department of Medicine, 3Department of Neurosurgery, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

ABSTRACT

Objectives: To evaluate the effectiveness of endovascular treatment (EVT) for acute ischaemic stroke in terms of angiographic results and clinical outcomes.

Methods: Patients who presented with symptoms of acute ischaemic stroke and who underwent EVT including mechanical thrombectomy and/or intra-arterial thrombolysis (IAT) at an acute-care public hospital between January 2013 and October 2016 were recruited. Digital angiographic images were reviewed by an independent neuroradiologist, who assigned a Thrombolysis in Cerebral Infarction (TICI) grade to each patient. Medical records were reviewed to retrieve the National Institutes of Health Stroke Scale score, modified Rankin scale (mRS) score at 90 days, and clinical outcomes.

Results: Records of a total of 38 patients were reviewed (mean age, 65.6 years). In all, 19 patients were treated with aspiration thrombectomy alone, 11 with both stent retriever and aspiration thrombectomy, six with stent-retriever thrombectomy alone, one with aspiration thrombectomy and IAT, and one with IAT alone. Revascularisation was successful (TICI grade 2b/3) in 76% of patients. The median time to reperfusion from the start of the procedure was 1 hour 3 minutes. Post-procedural symptomatic intracranial haemorrhage occurred in 11% of patients. Outcome was good (mRS score ≤ 2) and fair (mRS score ≤ 3) at 90 days in 27% and 43% of patients, respectively. The mean length of hospital stay for patients with successful and unsuccessful revascularisation was 35.7 and 62.3 days, respectively. The mortality rate within 90 days of EVT was 8%.

Conclusion: Our study shows that EVT has a high success rate for recanalisation, overall patient clinical outcomes are acceptable, and the procedure-related complication and mortality rates are low.

Key Words: Endovascular procedures; Stents; Stroke/diagnosis; Thrombectomy/methods

Correspondence: Dr DCW Tang, Department of Radiology, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong. Email: tca717@ha.org.hk

Submitted: 20 Apr 2017; Accepted: 6 Jun 2017.

Disclosure of Conflicts of Interest: As an editor of this journal, JCH Tse was not involved in the peer review process of this article. All other authors have no conflicts of interest to disclose.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
INTRODUCTION

Cerebrovascular disease is the second most common cause of death and disease burden (measured as disability-adjusted life years) worldwide in persons older than 60 years. In Hong Kong, it is one of the three most common causes of hospital admission and accounts for the largest number of hospital bed-days, leading to a considerable disease and disability burden.

Intravenous (IV) tissue plasminogen activator (tPA) given within 4.5 hours of symptom onset provides effective reperfusion therapy and has proven efficacy for acute ischaemic stroke. For some patients, however, IV-tPA is not appropriate owing to delayed presentation and contraindications such as coagulation disorder, recent surgery, or a history of intracranial haemorrhage. Furthermore, IV-tPA is less effective in treating proximal large-vessel occlusions.

Endovascular treatment (EVT) has some advantages over IV therapy. First, it achieves a better revascularisation rate than IV-tPA. Second, revascularisation can be achieved by mechanical means in some cases, without the use of thrombolytic agents. The techniques and knowledge in EVT are rapidly evolving, but there is a lack of published literature on EVT use in Hong Kong. This hospital audit study reports local experience of endovascular management of acute ischaemic stroke using endovascular techniques: mechanical thrombectomy and intra-arterial thrombolysis (IAT).

METHODS

Records of patients who presented to the Pamela Youde Nethersole Eastern Hospital, Hong Kong—an acute-care public hospital—with symptoms of acute ischaemic stroke and who underwent EVT including mechanical thrombectomy and/or IAT between January 2013 and October 2016 were retrospectively and anonymously reviewed.

Patient Characteristics

Patient characteristics including age, sex, vascular risk factors, time of stroke onset, time of accident and emergency department arrival, site of occlusion, baseline National Institutes of Health Stroke Scale (NIHSS) score, and modified Rankin scale (mRS) score were recorded. Patients were aged 18 years or older (no upper age limit), with reasonable pre-stroke functional ability and mRS score of ≤2, and established large-vessel occlusion in either the anterior or posterior circulation, according to findings from computed tomography angiography. There was no lower limit for the NIHSS score.
score, as long as computed tomography angiography confirmed large-vessel occlusion. Initiation of EVT had to be possible within 6 hours of stroke onset for anterior circulation stroke and within 12 hours for posterior circulation stroke. For patients in whom there was no contraindication to IV-tPA, tPA was administered before EVT. The main exclusion criterion on imaging was evidence of a large ischaemic core, as indicated by an Alberta Stroke Programme EarlyComputed Tomography Score (ASPECTS) of <7 on non-contrast computed tomography (ASPECTS values range from 0 to 10, with higher values indicating less infarct burden). Patients were also excluded if they had poor pre-stroke functional ability with an mRS score of ≥3, or a medical condition in which EVT was contraindicated, such as haemodynamic instability due to either a cardiovascular condition or severe renal impairment.

**Intervention**

Treatment characteristics including means of intervention, time of puncture and end of procedure were documented. An independent neuroradiologist reviewed all digital angiography records and assigned a Thrombolysis in Cerebral Infarction (TICI) grade to each patient, from grade 0 (no reperfusion) to grade 1 (minimal reperfusion), grade 2a (partial reperfusion in less than two-thirds of the vascular territory), grade 2b (complete reperfusion of the expected vascular territory but slower than normal), and grade 3 (prompt complete reperfusion).7 We extended the criteria for grade 2b to include reperfusion in at least two-thirds of the vascular territories.

**Technique**

Cerebral vessel access was established using a guiding sheath: either a 6-F Neuron Max 088 (Penumbra, Alameda [CA], USA) or, less commonly, a 6-F Shuttle (Cook, Bloomington [IN], USA). For extra support, the guiding sheath was advanced as distally as possible along the internal carotid artery for anterior circulation stroke, usually at the subpetrous segment. For patients with posterior circulation stroke, the guide sheath was advanced up to the distal cervical segment of the vertebral artery (VA).

The first technique of EVT was primary aspiration thrombectomy with ADAPT (A Direct Aspiration First Pass Technique).8 Under roadmap assistance, a 5MAX ACE reperfusion catheter (Penumbra, Alameda [CA], USA) was advanced to the face of the clot over a microcatheter—a 3MAX reperfusion catheter (Penumbra, Alameda [CA], USA)—and a 0.014-inch Synchro microguidewire (Stryker Neurovascular, Fremont [CA], USA) or a 0.016-inch Fathom microguidewire (Boston Scientific Corp, Naidich [MA], USA). The microguidewire and the microcatheter were advanced gently across the clot followed by advancement of the 5MAX ACE reperfusion catheter. Once the latter was immediately proximal to the clot, the microcatheter and microguidewire were removed. After 2 to 5 minutes of continuous aspiration using the Penumbra aspiration pump (Penumbra, Alameda [CA], USA), the 5MAX ACE reperfusion catheter was slowly withdrawn under continuous aspiration. During the study period, there was a gradual technical improvement of the large-bore reperfusion catheter to enhance clot extraction. At our institution, the 5MAX ACE reperfusion catheter (inner diameter of the distal lumen, 0.060 inch) was replaced in June 2015 with the newer-generation ACE 64 reperfusion catheter (inner diameter, 0.064 inch) and again in October 2016 with the ACE 68 reperfusion catheter (inner diameter, 0.068 inch).

The second technique involving the use of 5MAX ACE reperfusion catheter was combined aspiration with stent-retriever (stentriever) thrombectomy using a Trevo ProVue stent retriever (Stryker Neurovascular, Fremont [CA], USA) or Solitaire stent retriever (Medtronic, Dublin, Ireland). After establishing cerebral vascular access as described above, a microcatheter for stent-retriever delivery was placed within the 5MAX ACE reperfusion catheter and advanced to the site of occlusion under roadmap assistance. The 5MAX ACE reperfusion catheter was advanced as distally as was safely possible. The microguidewire and microcatheter were advanced through and beyond the thrombus. The stent was deployed over the thrombus by unsheathing the microcatheter to allow the close-cell self-expanding nitinol to oppose the vessel wall. After 2 to 5 minutes, the stent was pulled into the distal access catheter while applying simultaneous continuous aspiration to the 5MAX ACE reperfusion catheter using the Penumbra aspiration pump. Additional thrombectomy attempts were performed as needed.

**Outcomes and Complications**

The primary outcome was the mRS score at 90 days; the mRS is a 7-point scale ranging from 0 (no symptom) to 6 (death). A score of ≤2 indicates functional independence.9 The secondary outcomes included the NIHSS score on hospital discharge; the NIHSS assesses neurological deficit in 11 neurological categories, with
scores ranging from 0 (no deficit) to 42. Symptomatic intracranial haemorrhage was defined as neurological deterioration (an increase of ≥4 points in the NIHSS score) and evidence of intracranial haemorrhage on imaging studies.

RESULTS
Demographic and Clinical Characteristics
A total of 38 patients were treated with EVT between January 2013 and October 2016. There were 17 (45%) men and 21 (55%) women, with a mean (standard deviation [SD]) age of 65.6 (12.2) years. Most patients had severe stroke, with a median NIHSS score of 22 (interquartile range [IQR], 15-26) on hospital admission. Of the 38 cases of occlusion, 82% occurred in the anterior circulation. Hypertension was the most common vascular risk factor. There were 12 patients who had no vascular risk factor (Table 1).

Technical Aspects and Angiographic Outcomes
For most patients (95%), computed tomography angiography of the circle of Willis was performed before initiation of EVT. General anaesthesia was used in two (5%) patients, and local anaesthesia or conscious sedation in the others (95%). A simultaneous second revascularisation procedure, using a Carotid Wallstent (Boston Scientific, Natick [MA], USA) for cervical carotid stenting, was performed in two (5%) patients.

A total of 19 (50%) patients were treated with aspiration thrombectomy alone, 11 (29%) with both stent-retriever and aspiration thrombectomy, six (16%) with stent-retriever thrombectomy alone, one (3%) with aspiration thrombectomy and IAT, and one (3%) with IAT alone. Intravenous thrombolysis with alteplase administration was performed in 15 (39%) patients. The number of passes (either aspiration or mechanical thrombectomy) per patient ranged from 1 to 17 (median, 3 passes).

There was a gradual change in practice during the 4-year period from 2013 to 2016. In 2013, only three EVTs were performed, with one patient using a stent retriever, one using IAT alone, and one using aspiration thrombectomy and IAT. In 2014, four patients were treated with aspiration thrombectomy and two patients with a stent retriever. In 2015, there were nine patients treated with aspiration thrombectomy and three patients with a stent retriever. In 2016, a stent retriever was more commonly used (in 11 patients), whereas only six patients were treated with aspiration thrombectomy.

Both Trevo ProVue and Solitaire stent retrievers were used sequentially in two patients. Trevo ProVue stent retriever alone was used in 14 patients, and Solitaire stent retriever alone in one patient.

Outcomes and Complications
Revascularisation was successful (TICI grade 2b/3) in 29 (76%) patients (Figure 1). The success rate was 84% and 43% in anterior and posterior circulation stroke, respectively. The median time from symptom onset to initiation of procedure was 3 hours 22 minutes (3 hours 20 minutes for anterior circulation stroke; 5 hours 30 minutes for posterior circulation stroke). The reperfusion time from the start of the procedure was well documented in only 22 patients, and the median reperfusion time was 1 hour 3 minutes (Table 2).

Post-procedural symptomatic intracranial haemorrhage occurred in four (11%) patients (Figure 2). Intraprocedural haemorrhage in two patients was detected as contrast extravasation during attempts to navigate the Synchro microguidewire and 3MAX reperfusion catheter through the occluded vessels. Inadvertent dissection of the left VA in another patient was noted during the procedure. During navigation of the Synchro microguidewire and 3MAX reperfusion catheter coaxially placed within the 5MAX ACE reperfusion catheter into the left VA, the Neuron MAX was kicked back from the VA origin to the aortic arch, resulting in...
non-flow and limiting dissection at the proximal cervical left VA. A good outcome (mRS score ≤ 2) and a fair outcome (mRS score ≤ 3) at 90 days were achieved in 27% and 43% of patients, respectively. A similar good outcome (mRS score ≤ 2) at 90 days was achieved in anterior (27%) and posterior (29%) circulation strokes. A similar fair outcome (mRS score of 3) at 90 days was also achieved in the anterior (43%) and posterior (43%)

Table 2. Duration of steps in the endovascular treatment pathway

<table>
<thead>
<tr>
<th>Individual step</th>
<th>Median (h:min)</th>
<th>Interquartile range (h:min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from stroke onset to hospital admission</td>
<td>0:52</td>
<td>0:40-1:13</td>
</tr>
<tr>
<td>Time from hospital admission to start of procedure</td>
<td>2:15</td>
<td>1:30-3:26</td>
</tr>
<tr>
<td>Time from start of procedure to reperfusion</td>
<td>1:03</td>
<td>0:41-1:26</td>
</tr>
<tr>
<td>Time from start of procedure to end of procedure</td>
<td>1:35</td>
<td>1:00-2:20</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>1:32</td>
<td>1:01-2:08</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>3:00</td>
<td>0:50-4:05</td>
</tr>
<tr>
<td>Composite timings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from onset to start of procedure</td>
<td>3:22</td>
<td>2:30-4:12</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>3:20</td>
<td>2:22-3:55</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>5:30</td>
<td>4:05-6:02</td>
</tr>
<tr>
<td>Time from onset to end of procedure</td>
<td>4:47</td>
<td>4:20-6:28</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>4:40</td>
<td>4:02-5:45</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>7:10</td>
<td>6:20-8:10</td>
</tr>
</tbody>
</table>

Figure 1. A 56-year-old woman with good past health presenting with acute left-sided weakness and numbness. (a) Plain computed tomography (CT) scan of the brain demonstrated hyperdense right middle cerebral artery (MCA) sign (arrow), suggestive of acute right MCA thrombosis. (b,c) CT angiogram confirmed truncation of right M1 (arrow), with markedly decreased vascularity in right MCA territory and poor collaterals. (d,e) Cerebral digital subtraction angiogram (DSA) showed occlusion of right M1 (arrow) with absent distal flow. Thrombectomy with ADAPT (A Direct Aspiration First Pass Technique), using 5MAX ACE catheter and Penumbra aspiration pump was performed for 2 minutes. (f,g) Post-thrombectomy cerebral DSA showed restoration of the right MCA blood flow with no residual filling defect detected (Thrombolysis in Cerebral Infarction grade 3). Right A1 was taken over by contralateral anterior cerebral artery as confirmed by DSA of the left common carotid artery (not shown). (h) Follow-up plain CT scan of the brain showed only a small area of infarct in the right basal ganglia (arrows). The patient made an uneventful recovery and was discharged 10 days after the stroke, with modified Rankin scale score and National Institutes of Health Stroke Scale score improving from 5 to 1 and 16 to 1, respectively.
circulation strokes.

Among 29 patients with successful revascularisation (TICI grade 2b/3), 23 (79%) had an improved NIHSS grade on hospital discharge compared with that on admission, with a mean decrease of 14.4 (range, 3-28). On the contrary, only three of nine patients with unsuccessful revascularisation showed improvement in NIHSS score, with a mean of 4 and a range of 2 to 7.

The mean length of hospital stay for all patients was 42.0 days. The mean length of hospital stay for successful and unsuccessful revascularisation was 35.7 (IQR, 53.5) and 62.3 (IQR, 49.0) days, respectively. Thromboembolic disease was rare within 90 days of EVT, including two (5%) patients with both deep-vein thrombosis and pulmonary embolism and one (3%) patient with clinically suspected pulmonary embolism. Mortality was 8% (three patients) within 90 days of EVT and was due to hospital-acquired pneumonia (posterior circulation stroke) in one patient, clinically suspected acute pulmonary embolism (anterior circulation stroke), and failed thrombectomy in a patient with brainstem infarction. These patients were not related to the two patients with intra-procedural haemorrhage or the patient with VA dissection.

**DISCUSSION**

Our study showed that EVT for acute ischaemic stroke is safe and effective at our centre, with a reperfusion (TICI grade ≥ 2b) rate of 76%, good recovery (mRS score ≤ 2) in 27%, and 8% mortality within 90 days. These outcomes compare favourably to those of published studies, as summarised in a recent systematic review that showed recanalisation rates of between 25% and 96%, mean mortality of 17% (range, 7%-45%), and mean 90-day mRS score of ≤2 in 39% of patients (range, 15%-54%).

---

*Figure 2. An 81-year-old woman with hypertension and atrial fibrillation presenting with acute left-sided weakness and slurring of speech. (a) Computed tomography (CT) angiogram demonstrated absent vessels in the right middle cerebral artery (MCA) territory. (b,c) CT angiogram showed truncation of the right M1 (curved arrow) in early arterial phase. (d) Mechanical thrombectomy using Trevo ProVue stent retriever (arrows) was performed twice. (e,f) Post-procedural cerebral digital subtraction angiogram showed partially revascularised right M1 (curved arrow) and MCA branches (Thrombolysis in Cerebral Infarction grade 2a). (g) Follow-up plain CT scan of the brain 1 day after stroke showed extensive right MCA territory infarct with midline shift to the left side. (h) Mixed intracerebral haemorrhage, subarachnoid haemorrhage, and contrast staining were visible in the right frontotemporal lobe and basal ganglia. The patient was hospitalised for 118 days, with static modified Rankin scale score of 5 and National Institutes of Health Stroke Scale score slightly improving from 22 to 15.*
There were only three (8%) intra-procedural complications, comprising one patient with carotid artery dissection and two with intra-procedural cerebral haemorrhage. This low rate shows that EVT is safe in the hands of an experienced operator.

One patient had only IAT performed without mechanical thrombectomy. Digital subtraction angiography showed occlusion at the basilar tip and P1 segment of bilateral posterior cerebral arteries. The aortic arch was very tortuous with a short brachiocephalic artery, making right VA catheterisation difficult. Placement of the 5MAX ACE reperfusion catheter at the right VA failed owing to difficult anatomy. A 5-F Headhunter 1 catheter (Cook, Bloomington [IN], USA) was therefore used as a guiding catheter at the right distal cervical VA. Attempted navigation of the velocity microcatheter (Penumbra) with the aid of a 0.014-inch Synchro microguidewire into the intracranial VA failed owing to the unstable guiding catheter (5Fr H1). Therefore, only intra-arterial tPA was given as treatment.

In 2013, the New England Journal of Medicine published three randomised controlled trials: SYNTHESIS12 (The intra-arterial Versus Systemic Thrombolysis for Acute Ischaemic Stroke), MR RESCUE13 (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy), and IMS III14 (Interventional Management of Stroke III). All three failed to show a significant benefit of endovascular strategies. Nonetheless, these trials had several well-recognised limitations, including inconsistent use of vascular imaging to confirm vessel occlusion before randomisation, variable use of IV-tPA in the endovascular therapy group, and reliance on less-effective and older-generation mechanical devices.

In 2015, five separate multicentre, prospective, randomised controlled trials supported the efficacy and safety of mechanical thrombectomy using a stent retriever in the treatment of acute ischaemic stroke. These trials were MR CLEAN15 (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands), EXTEND-IA16 (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial), ESCAPE17 (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times), SWIFT PRIME18 (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischaemic Stroke), and REVASCAT19 (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset). In addition, the benefit persisted regardless of the patient’s age, severity of stroke, and location of occlusion.20

A meta-analysis published in JAMA21 in November 2015 concluded that among patients with acute ischaemic stroke, EVT of mechanical thrombectomy when compared with standard medical care with IV-tPA was associated with improved functional outcomes and higher rates of angiographic revascularisation. There was, however, no significant difference in occurrence of symptomatic intracranial haemorrhage or all-cause mortality within 90 days.

The American Heart Association / American Stroke Association has updated its guidelines and now recommends EVT as the standard therapeutic option for patients with demonstrable large-vessel occlusion and who present within 6 hours of symptom onset.22

The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES)23 pooled 1287 patients enrolled in the five positive thrombectomy trials published in 2015. The HERMES investigators concluded that in patients with large-vessel ischaemic stroke, earlier treatment with endovascular thrombectomy plus medical therapy compared with medical therapy alone was associated with a lower degree of disability at 3 months; immediate benefit became non-significant after 7.3 hours.

In one of the earliest local studies of EVT, in 2013 by Wong et al, IAT was the primary treatment while mechanical thrombectomy was considered adjunctive.24 On the contrary, only two patients were given IAT in our study. The practice of EVT also changed at our centre from 2013 to 2016. In the early era of EVT in 2013, the method of choice was heterogeneous, with two patients receiving IAT. ADAPT was the dominant EVT modality in 2014 and 2015. In 2016, following publication of the five 2015 trials that confirmed the efficacy of stent-retriever thrombectomy in acute ischaemic stroke, we performed this procedure in most of our patients.

Local anaesthesia or conscious sedation was used for
most of our patients, with only two patients receiving general anaesthesia to protect their airway. One patient vomited in the angiography suite prior to thrombectomy, and the other had a basilar artery thromboembolism with a Glasgow Coma Scale score of 3/15. Conscious sedation is preferred by some interventional radiologists because it can be delivered much faster. A retrospective analysis of 2512 patients concluded that in thrombectomy patients who received conscious sedation, there was decreased in-hospital mortality, a decreased rate of pneumonia, lower hospital costs, and shorter length of stay compared with those who received general anaesthesia.25 According to one recent single-centre prospective randomised clinical trial (SIESTA study), conscious sedation did not result in better early neurological outcome compared with general anaesthesia.26 General anaesthesia is preferred for patients who are uncooperative or agitated, have a low consciousness level, or cannot protect their airway, and in most patients with posterior circulation stroke.27

Endovascular treatment is traditionally reserved for stroke patients with a higher NIHSS score (8-10 or above). It is also known that a higher NIHSS score is associated with poorer clinical outcome and higher risk of intracerebral haemorrhage after treatment.28 The median NIHSS score of recruited patients in the five published 2015 trials was 13 to 18, whereas that of our patients was 22. This may partly explain why the functional outcome in our patients was poorer than that of patients in the 2015 trials. Furthermore, only anterior circulation stroke patients were recruited in the five 2015 trials, but there were seven patients with posterior circulation stroke included in our study.

The limitations of this study relate to the relatively small number of patients who presented at our single centre and the retrospective nature of the study. As in all real-world environments, patient selection criteria and treatment guidelines evolved during the 4-year study period in the wake of published randomised controlled trial results, and are most likely responsible for the heterogeneity in our patient population.

CONCLUSION

Our study has shown that EVT at our centre achieves a highly successful recanalisation rate and overall patient clinical outcomes are acceptable with low procedure-related complication and mortality rates. The favourable results in the recently published stroke trials had a major impact on our practice in acute stroke management. Further prospective studies or randomised controlled trials are required to answer some unresolved questions, such as the most optimal treatment device and management strategy for certain subgroups of patients, for instance posterior circulation stroke.

REFERENCES

16. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L,