Transmyocardial Laser Revascularisation

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Final assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which new medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC). The report was endorsed by the Commonwealth Minister for Health and Aged Care on 8 September 1999.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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The operation is performed on the beating heart without using the heart-lung circulation machine. Both CO_2 and holmium lasers can be used in this procedure. The CO_2 laser, produced by PLC Medical Systems, delivers a maximum power of 850 watts in pulses of 10 to 99 milliseconds at energies of eight to 80 joules. It remains unclear whether the devices which use different laser sources are different in terms of clinical performance.

Medicare Services Advisory Committee – role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. The medical literature on the new technology is searched and the evidence is assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence. A supporting committee with expertise in this area evaluates the evidence and provides advice to MSAC.

MSAC's assessment of transmyocardial laser revascularisation

MSAC's assessment is based primarily on two randomised controlled trials (NHMRC Level II). However, two systematic reviews based on uncontrolled clinical studies were also included in the assessment (NHMRC Level IV).

Clinical need

Data from the Australian Institute of Health and Welfare indicates that in Australia heart disease, of which ischaemic heart disease is a high proportion, affects 23.8 females per 1,000 and 32.3 males per 1,000. Heart disease remains the biggest killer in Australia: 1996 mortality data shows there were 17,765 deaths in females and 29,637 in males due to ischaemic heart disease. There is a lack of data to indicate the incidence of hospital admission for refractory or unstable angina.

The application estimates approximately 50–100 patients will need TMR each year in a large teaching hospital providing this service, with no more than 400 procedures per year in Australia. However, expert opinion indicates this is likely to be an underestimation of usage.

Safety

TMR is associated with 3–5 per cent peri-operative mortality and the common complications associated with any thoractomy.

Effectiveness

In two CO_2 laser randomised controlled trials, TMR was associated with a significant reduction in the severity of angina, with 39 per cent more patients experiencing reduced angina severity by at least two classes in the Canadian Cardiovascular Society Classification of Angina. Consequently, consumption of anti-anginal medication was also significantly reduced. A significant reduction in the incidence of unstable angina, by 69 per cent, was also reported in one RCT. However, clinical benefits of avoiding acute myocardial infarction, increasing exercise tolerance, and prolonging survival were not demonstrated. In addition, there is uncertainty as to whether effective symptom relief is sustained beyond 12 months.

Cost effectiveness

Based on the PLC Medical Systems RCT, the estimated incremental cost effectiveness ratios for the first year after TMR are:

- $18,159 per extra patient free of unstable angina; and
- $21,237 per extra patient free of disabling angina.

Cost savings of up to $4,297 per patient per year may occur for the second year and subsequent years of follow-up, if there is sustained symptom relief.

Need for further data

Further information on the long-term effectiveness and cost-effectiveness of TMR would be particularly valuable in establishing the clinical role of this technology: this may be obtained from Australian and overseas studies currently being undertaken. In addition, it would be useful to compare outcome data from the holmium laser with that from the CO_2 laser.

Recommendation

MSAC found there is insufficient evidence to conclude that the clinical benefits of TMR outweigh the potential risks as:

- the procedure is associated with 3–5 per cent peri-operative mortality; and
- there is uncertainty in symptom relief beyond 12 months.

In addition, the cost effectiveness ratios are considered unfavourable.

MSAC therefore recommends that public funding for TMR should not be supported at this time.

Introduction

The Medicare Services Advisory Committee (MSAC) has assessed transmyocardial laser revascularisation (TMR), which is a therapeutic procedure for refractory angina. MSAC evaluates new health technologies and procedures for which funding is sought under the Medicare Benefits Scheme (MBS) in terms of their safety, effectiveness and cost-effectiveness, taking into account other issues such as access and equity. MSAC uses an evidence-based approach for its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are shown in Appendix A. MSAC is a multidisciplinary expert body, with members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics and health administration.

This report summarises the assessment of current evidence for using TMR as a therapeutic procedure for treating refractory angina.

Background

Transmyocardial laser revascularisation

The procedure

Transmyocardial laser revascularisation (TMR) is a procedure that mimics the circulation of the reptilian heart by creating 20–40 myocardial channels in the left ventricle using laser ablation. It is hypothesised that the channels remain open and are able to perfuse ischaemic areas of the heart with oxygen-rich blood. However, the mechanisms of action are still unclear.

The operation is performed on the beating heart without using the heart-lung circulation machine. The majority of studies and trials used the PLC Medical Systems' CO_2 laser, which delivers a maximum power of 850 watts in pulses of 10 to 99 milliseconds at energies of eight to 80 joules. A holmium laser, manufactured by CardioGenesis, has also been used. It remains unclear whether the devices, which use different laser sources, are different in terms of clinical performance.

The estimated average intensive care unit/critical care unit (ICU/CCU) stay following the procedure is 2 ± 3 days, and the average hospital stay is 8 ± 6 days.

Intended purpose

TMR is indicated for patients who suffer from refractory angina, that is severe angina: Canadian Cardiovascular Society (CCS) Class III or IV (Table 1), and who are not suitable for coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Table 1 Canadian Cardiovascular Society Classification of Angina

Class	Activity evoking angina	Limits to normal activity
I	prolonged exertion	none
II	walking > 2 blocks	slight
III	walking < 2 blocks	marked
IV	minimal or rest	severe

Source: Campeasu [1]

The unsuitability for CABG or PTCA could be due to diffuse coronary atherosclerosis, distal stenoses, small coronary arteries, or inability to undergo another CABG or PTCA. As the efficacy of anti-anginal medication is not sustained, patients are left with severe disabling angina (Class III or IV) and have no other treatment options.

TMR should be performed in large teaching hospitals by cardiothoracic surgeons who are trained in the technique.

Clinical need / burden of disease

Data from the Australian Institute of Health and Welfare indicates that in Australia heart disease, of which ischaemic heart disease is a high proportion, affects 23.8 females per 1,000 and 32.3 males per 1,000 (1995 survey data).[2] Heart disease remains the biggest killer in Australia: 1996 mortality data[3] shows there were 17,765 deaths in females and 29,637 in males due to ischaemic heart disease. There is a lack of data to indicate the incidence of hospital admission for refractory or unstable angina.

The application estimates approximately 50–100 patients will need TMR each year in a large teaching hospital providing this service, with no more than 400 procedures per year in Australia. However, expert opinion indicates this is likely to be an underestimation of usage.

TMR offers a treatment option for patients with refractory angina where other treatment modalities either failed or are unsuitable.

Existing procedures

For patients who suffer from refractory angina and who are not suitable for CABG or PTCA, medical management including anti-anginal drugs and supportive care is commonly used.

A direct substitution or replacement of other therapies is not expected. However, TMR is likely to reduce the use of anti-anginal drugs in this group of patients.

Comparator

Medical management, including anti-anginal drugs and supportive care, is considered the appropriate comparator for TMR.

Marketing status of the devices used in the procedure

The devices used in TMR, that is the Heart Laser™ kit (CO_2 laser) manufactured by PLC Medical Systems and the holmium laser manufactured by CardioGenesis, are currently listed on the Australian Register of Therapeutic Goods. Before listing, sponsors must submit information, such as labelling, product literature and, for certain categories, evidence of quality systems compliance, compliance with standards and test certificates, to the Therapeutic Goods Administration (TGA) for assessment.

The Heart Laser™ (CO_2 laser) has been granted premarket approval by the United States Food and Drug Administration (FDA). The approved indication is for treating ischaemic heart disease in patients who are not candidates for conventional CABG or PTCA revascularisation. FDA approval of CardioGenesis (holmium laser) is pending.

Current reimbursement arrangement

Currently there is no specific MBS item number for TMR.

Approach to assessment

MSAC reviewed the literature available on TMR and convened a supporting committee to evaluate the evidence of the procedure and provide expert advice.

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period 1986 to 1998. Searches were conducted through Medline, Cochrane Library and DARE databases.

The search terms used were 'transmyocardial revascularisation', 'transmyocardial laser revascularisation' and 'TMLR' with MESH terms of myocardial revascularisation, angina pectoris, coronary disease and laser surgery.

Articles included in this assessment are systematic reviews [4,5] and randomised controlled trials (RCTs)[6,7,8] of TMR for the treatment of refractory angina.

The evidence presented in the retrieved studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence (Table 2).

Table 2 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III–1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III–2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III–3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC [9]

Characteristics of the study

The design of the selected studies is shown in Table 3.

CO_2 Laser Trial[6] This was an open 'head-to-head', comparative trial, conducted in 12 clinical centres in the United States. The trial recruited 191 patients with refractory angina (CCS Class III or IV) but not suitable for CABG or PTCA. Patients with unstable angina were excluded. One hundred and ninety-one patients were randomly allocated 1:1 to TMR plus anti-anginal medication arm (n=91) or to medical management only arm (n=101). No detail is available regarding the randomisation method used. Patients were monitored at three, six and 12 months after TMR.

The trial was designed to allow patients in the medical management group to crossover to have TMR, if they suffered from an adverse clinical event and had been in the medical management group for at least six months.

In addition, patients with unstable angina, who otherwise met the study inclusion criteria, were enrolled in a third arm to undergo TMR. This arm is not considered relevant to support this application, and is excluded from further discussion.

Table 3 Characteristics of studies

Level of Evidence	Author	Study Design	Subjects
Level II	PLC Medical Systems[6]	CO_2 Laser Trial RCT ('head-to-head'), comparative trial, patients underwent either TMR plus anti-anginal medication or medical management, unblind design, follow-up: 12 months.	n=191 (with refractory angina – class III or IV but not suitable for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)
Level II	Schofield et al[7]	CO_2 Laser Trial RCT ('head-to-head'), patients underwent either TMR plus anti-anginal medication or medical management, unblind design, follow-up: 12 months.	n=188 (with class III or IV refractory angina and reversible ischaemia)
Level II	CardioGenesis[8]	Holmium Laser Trial RCT ('head-to-head'), patients underwent either TMR or anti-anginal medical therapy, unblind design, follow-up: 9 months.	n=181 (with severe stable angina but not suitable for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty)

RCT: randomised controlled trial; TMR: transmyocardial laser revascularisation

CO_2 Laser Trial[7] The trial was an open randomised trial with 'head-to-head' comparison. One hundred and eighty-eight patients with CCS Class III or IV refractory angina and reversible ischaemia evidenced by radionuclide myocardial perfusion scan were enrolled. Following a secure 1:1 randomisation, 94 patients were allocated to TMR plus anti-anginal medication arm, and 94 to medical management only arm. No crossover of treatment was allowed. Patients were monitored at three, six and 12 months after TMR.

Holmium Laser Trial[8] This trial is a randomised 'head-to-head' controlled, multi-centre trial, conducted in 19 centres in the United States. One hundred and eighty-one patients with severe stable angina but not suitable for CABG or PTCA were assigned to either TMR arm (n=91) or anti-anginal medical therapy arm (n=90). The method of randomisation was not detailed. The trial was unblind in design. Patients were followed up at three, six and nine months, with a mean follow-up period of nine months. The trial was ongoing at the time of preparing the interim report.

Patient characteristics

As reported in both CO_2 laser trials,[6,7] there appeared no statistically significant differences in baseline characteristics between the two treatment arms that might affect endpoint measurements.

Relevance to Australian setting

All the trials were considered to be representative of patient groups for whom funding is sought through the MBS.

'Intention-to-treat' analysis

The CO_2 laser trial by Schofield et al[7] and the interim report of the holmium laser trial[8] were not analysed on all patients randomly enrolled. The CO_2 laser trial reported the results on unstable angina and decrease of angina classes on an 'intention-to-treat' basis, but failed to analyse other outcome endpoints on 'intention-to-treat' principles. It is noted that as many as 50 per cent of patients (51/101) crossed over to TMR treatment after six months.

Due to lack of complete clinical data from other TMR trials (holmium laser trials by CardioGenesis and Eclipse TMR 2000), possible differences between laser devices in terms of clinical effectiveness, and the TGA approval status, this assessment report has focused on TMR performed using CO_2 laser.

Expert advice

A supporting committee, including members with expertise in relation to cardiology, cardiothoracic surgery and TMR, was convened to assess the evidence on the procedure. In selecting members for supporting committees, MSAC's practice is to approach appropriate medical colleges, associations or specialist societies for nominees. Membership of the supporting committee is shown in Appendix B.

Results of assessment

Is it safe?

TMR is associated with 3–5 per cent peri-operative mortality, and the common complications associated with any thoractomy.

Table 4 gives a profile of major reported adverse events of TMR and medical management (MM) in PLC Medical System's RCT.[6]

It should be noted that some complications are specific to thoractomy, such as cardiac arrhythmia, cardiogenic shock, pericarditis, pulmonary complications and ARDS.

Expert advice from the supporting committee is that a patient should not undergo TMR if he or she has had an episode of unstable angina during the preceding week.

Table 4 Adverse events

Event	Peri-operation TMR (n=91) %	Overall during 12 months TMR (n=91)	MM (n=101) %
Unstable angina	1.1	2.2	69.0
Acute myocardial infarction	5.5	6.6	12.0
Congestive heart failure	11.0	11.0	10.0
Pulmonary complications	8.0	8.0	2.0
Arrhythmia-atrial	2.0	2.0	n/a
Arrhythmia-ventricular	10.0	10.0	n/a
Cerebrovascular accident	1.0	1.0	n/a
Cardiogenic shock	1.1	1.1	n/a
Left ventricular bleeding	1.1	1.1	n/a
Cerebrovascular complications	1.1	n/a	n/a
Pericarditis	n/a	1.1	n/a
Anaemia	3.3	n/a	n/a
Adult respiratory distress syndrome	1.1	n/a	n/a
Laser hit induced mitral regurgitation	1.1	1.0	n/a
Peri-operative mortality	PLC[6] CO_2	3.3%	
	Schofield[7] CO_2 laser trial	5.0%	
	Mean of six studies, UHC review[4]	9.6% (3–20%)	

TMR: transmyocardial laser revascularisation; MM: medical management; n/a: not applicable

Is it effective?

Based on available data from the systematic reviews MSAC concluded that TMR appeared to have an acceptable survival rate, effectively relieved angina, and improved quality of life. However, there was insufficient evidence to show improvement in myocardial perfusion, cardiac function and long-term efficacy. The requirement for further information from an RCT was acknowledged.

Two RCTs using CO_2 laser have since been identified. The main outcome measures were: change in angina severity, incidence of unstable angina, quality of life, reversible perfusion defects, exercise tolerance, incidence of acute mycocardial infarction (AMI), and 12 month survival.

Definition of endpoints

Angina score: in the RCT by Schofield et al,[7] chest pain was also recorded by patients on an 11–point scale,[10] with 0 as no pain and 10 as bad as the pain could be.

Angina class: was assessed according to the CCS angina classification system. It should be noted that this is a subjective endpoint.

Quality of life: was measured by two questionnaires independently filled out by patients—the Short Form 36 (SF-36) and the Seattle Angina Questionnaire (SAQ). Again, the scores are subjective parameters, and are heavily influenced by angina severity.

Reversible perfusion defect: the detection of reversible perfusion defects was not included in the interim report of the holmium laser trial.[8] Different methods were used to identify reversible perfusion defects in the two CO_2 laser trials.[6,7]

PLC Medical Systems Trial:[6] reversible perfusion defects were detected using dipyridamole thallium-201 single photon emission computerised tomography. For stress versus redistribution at rest, perfusion images were acquired during a stress study 10 to 20 minutes after thallium-201 injection, and three to four hours later at rest. For stress versus reinjection, thallium-201 was readministered 10 to 20 minutes following the above study. The heart was divided into three slices to represent the apical, middle and basal thirds of cross-sectional myocardium. These three slices were further divided into eight segments each, ie a total of 24 segments. A relevant difference in thallium uptake between stress and redistribution/reinjection images was compared. Perfusion defects that appeared during the stress study but disappeared at rest were classified as 'reversible perfusion defects'.

RCT by Schofield et al:[7] Technetium-99 scanning was used in the two-day rest–stress protocol. Technetium-99 administration and imaging were undertaken on day one at rest, and on day two at peak stress. The left ventricle was divided into five segments; anterior, inferior, lateral, apex, and septum. Segments having decreased Technetium-99 uptake during stress compared with at rest were identified as reversible perfusion defects.

Survival: presented in Kaplan-Meier curves at baseline and up to 12 months after TMR in both CO_2 laser RCTs.[6,7]

Unstable angina: patients were classified as having unstable angina if they required ICU/CCU hospitalisation with intravenous anti-anginal medication for at least 48-hours.

Exercise tolerance: not defined nor were details provided of how this was measured in PLC Medical Systems RCT.[6] In the RCT by Schofield et al,[7] a treadmill test and 12-minute walk were performed. The time on the treadmill and the onset of angina during the treadmill test was recorded. The distance, the incidence of angina and requirement for nitrates were monitored during the 12-minute walk.

Clinical results

RCT results are summarised in Table 5. Note that there are limited data available for the RCT using holmium laser.[8]

Data on quality of life, using SF-36 and SAQ instruments demonstrated similar results. The detailed results from SF-36 are included in Table 5.

Table 5 Clinical results – TMR vs Medical Management

Endpoint	TMR		Medical Management	
Angina class	% pts had decreased ≥2 angina classes		% pts had decreased ≥2 angina classes	
PLC[6] CO_2 laser RCT	(n=78) at 3 months	67%[a]	(n=64) at 3 months	6%
	(n=67) at 6 months	67%[a]	(n=47) at 6 months	6%
	(n=71) at 12 months	72%[a]	(n=23) at 12 months	12%
Schofield[7] CO_2 laser RCT	(n=79) at 3 months	34%[a]	(n=70) at 3 months	3%
	(n=70) at 6 months	22%[a]	(n=67) at 6 months	4%
	(n=74) at 12 months	25%[a]	(n=78) at 12 months	4%
Holmium laser RCT[8]	Baseline vs 6 months (class mean)		Baseline vs 6 months (class mean)	
	3.79 1.83		3.65 3.61	
Quality of life (change from baseline)				
PLC[6] CO_2 laser RCT	SF-36 (physical component)		SF-36 (physical component)	
	at 3 months	+9[a]	at 3 months	–1
	at 6 months	+10[a]	at 6 months	+3
	at 12 months	+9[a]	at 12 months	+2
	SF-36 (mental component)		SF-36 (mental component)	
	at 3 months	+10[a]	at 3 months	–2.5
	at 6 months	+8[a]	at 6 months	+2
	at 12 months	+10[a]	at 12 months	+1
Schofield[7] CO_2 laser RCT	n/a		n/a	
Holmium laser RCT[8]	n/a		n/a	
Reversible perfusion defect				
PLC[6] CO_2 laser RCT	at 3 months	–1.55±0.5[a]	at 3 months	–0.75±0.5
(average number)	at 6 months	–0.85±0.5[a]	at 6 months	–0.7±0.5
	at 12 months	–1.45±0.5[a]	at 12 months	1.45±1.0
Schofield[7] CO_2 laser RCT	baseline	144/460 (31%)	baseline	160/469 (34%)
(overall number/overall %)	3 months	79/404 (20%)	3 months	104/430 (24%)
	6 months	87/400 (22%)	6 months	94/405 (23%)
	12 months	78/370 (21%)	12 months	86/399 (22%)
Holmium laser RCT[8]	n/a		n/a	
Exercise tolerance				
PLC[6] CO_2 laser RCT	n/a		n/a	
Schofield[7] CO_2 laser RCT	**treadmill test** (time in seconds, compared with medical management group)			
	at 3 months	+43 s(–5,91)		
	at 6 months	36s(–7,83)		
	at 12 months	+40s(–15,94)		
	12 minute walk (distance in metres over 12 minutes, compared with medical management group)			
	at 3 months	NS		
	at 6 months	NS		
	at 12 months	+3m[a](–7,74)		
	(overall distance: p=0.022)			
Holmium laser RCT[8]	at 6 months	45% improvement	at 6 months	no change
Survival				
PLC[6] CO_2 laser RCT	at 12 months	85% NS	at 12 months	79%
Schofield[7] CO_2 laser RCT	at 12 months	89% (83–96%) NS	at 12 months	96% (92–100%)
Holmium laser RCT[8]	at 9 months	5 deaths (n=91)	at 9 months	6 deaths (n=90)
Acute myocardial infarction				
PLC[6] CO_2 laser RCT	10% (9/91) NS		20% (8/41)	
Schofield[7] CO_2 laser RCT	n/a		n/a	
Holmium laser RCT[8]	n/a		n/a	
Unstable angina				
PLC[6] CO_2 laser RCT	incidence over 2 months 0.02% (2/91)[a] ICU/CCU admission over 12 months 0.02 (mean)[a]		incidence over 12 months 69.3% (70/101) ICU/CCU admission over 12 months 1.37 (mean)	
Schofield[7] CO2 laser RCT	ICU/CCU admission over 12 months 0.5/patient (0.3–0.6)[a]		ICU/CCU admission over 12 months 0.8/patient (0.6–0.9)	
Homium laser RCT[8]	n/a		n/a	

[a] statistically significant difference between the treatment arms; NS: not statistically significant; SF: short form; ICU/CCU: intensive care unit/critical care unit

Meta-analysis

The characteristics of the patient populations recruited into the CO_2 laser TMR trials[6,7] were considered comparable. However, due to different endpoints and outcome measures used, combining results by means of meta-analysis (random effect model) was only attempted for two common endpoints used: ie decrease in CCS angina class and survival at 12 months. The results are presented in Table 6. The decrease in angina severity remained significant in patients who had received TMR, whilst the difference in survival was not statistically significant.

Table 6 Combined results

Endpoint	TMR vs Medical Management		
CCS angina class decrease ³ 2	at 3 months 24.76	at 6 months 13.25	at 12 months 11.95
Odds ratio (95% CI)	(10.15–60.37)	(2.66–66.12)	(4.79–29.79)
p value	p<0.00001	p=0.0016	p<0.00001
Risk difference (95% CI)	45.8%	38.7%	39.7%
p value	(17.3%–74.2%)	(–4.2%–81.6%)	(3.5%–75.9%)
	p=0.0017	p=0.077	p=0.032
Survival at 12 months		0.70	
Odds ratio (95% CI)		(0.15–3.34)	
p value		p=0.66	

TMR: transmyocardial laser revascularisation; CCS: Canadian Cardiovascular Society; CI: confidence interval

The effect of cardioactive medication

To confirm that the observed symptomatic improvement in patients treated with TMR was not due to the effects of cardioactive medication, PLC Medical Systems[6] provided detailed data on anti-anginal medications. Patients were sub-grouped into angina success (improved) and angina failure (not improved), and changes in medication consumption were analysed. Three primary types of cardioactive medications, β-blockers, calcium channel blockers and nitrates, were monitored. The variation in medication was defined as 'decrease', 'increase' and 'no change'.

Decrease: the discontinuation of a medication or the halving of medication dose, or had more medication decreases than increases;

Increase: the addition of a new medication or doubling of medication dose, or had more medication increases than decreases; and

No change: also included patients without medication.

The analysis concluded there was no significant difference in consumption of cardioactive medication between patients with and patients without improved angina symptoms. Therefore, the relief of angina symptoms appeared to be due to TMR, but not cardioactive medications.

Change of cardioactive medications TMR vs Medical Management

From the data provided in the PLC Medical Systems RCT,[6] patients who underwent TMR took less cardioactive medication (β-blockers, calcium channel blockers and nitrates) than those treated with medical management.

At the end of 12 month follow-up, there was increased use of β-blockers, calcium channel blockers and nitrates in 15 per cent, 13 per cent and 24 per cent, respectively, of patients who underwent TMR. However, compared to the medical management group, the increase in the TMR group was not significant (Table 7).

Table 7 TMR vs Medical Management: change of cardioactive medications at the end of 12 months follow-up (PLC Medical Systems RCT)[6]

Medication	TMR n=79	Medical Management n=67	Difference (95% CI)
b-blocker			
decrease	22 (28%)	10 (15%)	12.3% (1.1%,26%) p=0.0061
no change	44 (56%)	46 (69%)	–12.9% (–1.9%,–24%) p=0.021
increase	13 (15%)	11 (16%)	0.04% (–8.5%,8.5%) p=0.99
Calcium channel blocker			
decrease	27 (34%)	5 (8%)	26.7% (18%,35%) p<0.00001
no change	42 (53%)	53 (79%)	–25.9% (–15%,–36%) p<0.0001
increase	10 (12.6%)	9 (13.4%)	–0.7% (–0.69%,–0.85%) p=0.84
Nitrates			
decrease	30 (38%)	9 (13%)	24.5% (15%,34%) p<0.00001
no change	30 (38%)	39 (58%)	–20% (–8.9%,–31.5%) p=0.00043
increase	19 (24%)	19 (29%)	–4.3% (–5.8%,–14.4%) p=0.40

TMR: transmyocardial laser revascularisation; CI: confidence interval

Similar results were reported by Schofield et al,[7] where a significant decrease in calcium channel blocker use was observed in patients who received TMR at 12 months post operation: 8 per cent experienced decrease in medication in the TMR group, whereas 6 per cent had an increase in the medical management group ($p<0.001$). Nitrate consumption was also reduced, the proportion of patients using these drugs fell from 86 per cent to 69 per cent in the TMR group. In comparison, in the medical management group the proportion of patients receiving nitrates increased from 79 per cent to 82 per cent ($p=0.025$).

Interpretation of results

The main outcomes are summarised in Table 8.

Table 8 Main outcomes

Level of evidence (MSAC guidelines)	Outcome	Number needed to treat
Level I	**angina class reduced ³ 2 classes at 12 months**	2.5
PLC and Schofield CO_2 laser trials[6,7]	39.7% (3.5%–75.9%) more patients in TMR group	
Level II	**free of disabling angina**	1.7
PLC CO_2 laser trial[6]	59% (41.5%–76%) more patients in TMR group	
Level II	**free of unstable angina**	1.4
PLC CO_2 laser trial[6]	69% (57.6%–76.6%) more patients in TMR group	
Level II	**improved quality of life (SF – 36)**	not available
PLC CO_2 laser trial[6]	+8 to+10 vs –2.5 to +3	
Level II	**reversible perfusion defects at 12 months**	not available
PLC CO_2 laser trial[6]	mean: –1.45±0.5 vs 1.45±1.0 p≤0.03	
Schofield CO_2 laser trial[7]	overall %: 21% vs 22% p=0.975	

MSAC: Medicare Services Advisory Committee; TMR: transmyocardial laser revascularisation; SF: short form

The RCTs demonstrated that TMR:

- significantly reduced the severity of angina, 39 per cent more patients had reduced angina severity by at least two classes at the 12-month follow-up; [6,7]
- significantly reduced the incidence of unstable angina by 69 per cent, and reduced related hospitalisation by 1.35 episodes/patient/year;[6]
- significantly reduced the average number of reversible myocardial perfusion defects;[6] and
- significantly improved patients' quality of life.[6]

It is noted that, in contrast to the results obtained by PLC Medical Systems,[6] the overall number of sites with reversible perfusion defects did not significantly differ between the TMR and medical management groups in Schofield's trial.[7] This may be due to the difference in segmentation methods and/or the scanning agents used in the trials.

Based on the data provided, TMR failed to reduce the incidence of AMI or to prolong survival. However, it is recognised that the trial was not empowered to detect such differences, given the sample size needed. To demonstrate a 10 per cent difference in AMI, 430 patients, 215 in each arm, are needed. Similarly, to detect a 6 per cent difference in survival, 720 patients, 360 patients in each arm, are needed.

It is uncertain as to whether the effectiveness in symptom relief is sustained beyond 12 months.

While there is clear evidence that TMR is associated with reduced angina and improved quality of life, some of this improvement may be due to a placebo effect. This is due to the inconsistent findings on myocardial perfusion and the unblinded nature of both trials. Nevertheless due to the size of the effect, the duration of the effect for 12 months, the reduction in use of anti-anginal medication and the reduction in ischaemic events, much of the treatment benefit is likely to be real.

What are the economic considerations?

A preliminary economic analysis has been conducted using a cost effectiveness analysis approach. Considering availability of data, the cost effectiveness analysis was based on information provided in PLC Medical Systems' RCT.[6]

Clinical Benefits

Unstable angina

The claimed clinical benefit used in the economic analysis is the significant reduction in incidence of unstable angina associated with TMR treatment, in comparison with medical management (0.02% compared to 69.3%). That is, 69 per cent (95% confidence interval: 57.6% – 76.6%) more patients are free of unstable angina at 12 months following TMR, compared with medical management. This results in a significantly reduced average number of ICU/CCU hospitalisations: 0.02 episodes compared to 1.37 episodes, over 12 months. The application provides no details to allow independent verification.

It is noted that, while the application did not use the results of the RCT, it presented the number of episodes of hospitalisation for unstable angina during the year before (2.5±2) and in the year after (0.3±0.6) the TMR operation in patients who had TMR, as the claimed clinical benefit. No explanation was provided as to why the RCT results were not used. By doing this, the amplitude of clinical benefit is increased from 1.35 (1.37–0.02) to 2.2 (2.5–0.3). This approach is unjustified and is biased in favour of TMR, and should not be regarded as valid.

Reduced angina severity

Seventy-two per cent (95% confidence interval: 41.5% – 76%) of patients in the TMR arm, compared with 13 per cent of patients in the medical management arm, had reduced angina severity by at least two classes. That is, 59 per cent more patients were free of disabling angina after TMR.

Quality of life

Although the RCT demonstrated an improvement in quality of life following TMR, insufficient information is available to present the health benefit in terms of quality adjusted life years. Therefore, a cost utility analysis could not be performed.

Costs of TMR and Medical Management

Cost in the first year

The costs incurred in the first year (based on RCTs[6,7,8]) are listed in Table 9.

Table 9 Costs associated with TMR and Medical Management

Item	Unit cost	TMR	Medical Management
TMR procedure	$10,748 (AN-DRG 227 public)	$10,748	$0
Hospitalisations for unstable angina	$2,994 (AN-DRG 269 public)	$2,994 x 0.02 = $59.88	$2,994 x 1.37 = $4,101.78
Anti-anginal medication	n/a	ND	ND
TMR equipment	$5,800 (US$3,500) (if exchange rate: 0.60)	$5,800	
Complications			
Acute myocardial infarction	$4,074 (AN-DRG 249 public)	$4,074 x 6.6% = $268.88	$4,074 x 12% = $488.88
Congestive heart failure	$3,482 (AN-DRG 252 public)	$3,482 x 11% = $383.02	$3,482 x 10% = $348.2
Pulmonary complication	$3,483.66 (mean of AN-DRG 169, 171 & 176 public)	$3,484 x 8% = $278.72 sub-total = $930.62	$3,484 x 2% = $69.68 sub-total = $906.76
Total		$10,748 + $59.88 + $930.62 + $5,800 = **$17,539**	$906.76 + $4,102 = **$5,009**

TMR: transmyocardial laser revascularisation; AN-DRG: Australian National Diagnostic Related Group; ND: no data is available to allow an estimate

Comments

The cost of anti-anginal medication is not included in the cost estimate, and this in fact favours the medical management arm.

The cost of the equipment for TMR should not be excluded in the economic analysis. It can be estimated at a rate of depreciation, or at a leasing rate as suggested by PLC Medical Systems.[6] The capital cost of Heart Laser™ is in the range of US$200,000 to US$500,000.

Under the leasing arrangement with PLC Medical Systems, a fee of US$3,500 or $5,800 per procedure will be charged. This fee is considered appropriate to be included in the economic analysis.

The costs, due to complications, are also included, though it seems unlikely to influence the result.

Cost during first three years

The total cost per year and cumulative costs over three years are calculated in the application and listed in Table 10.

Table 10 Cost comparison: TMR vs Medical Management

		Year 1		Year 2		Year 3	
		Secretariat	Applicant	Secretariat	Applicant	Secretariat	Applicant
TMR	TMR	$10,748.00					
	Unstable angina	$59.88		$59.88		$59.88	
	Complications	$930.62					
	Equipment	$5,800.00		$651.90		$860.94	
Total per year		$17,539.00	$11,646.00	$711.78		$711.78	
Cumulative cost		$17,539.00	$11,646.00	$18,250.00	$12,545.00	$18,961.00	$13,442.00
MM							
	Unstable angina	$4,101.78		$4,101.78		$4,101.78	
	Complications	$906.76		$906.76		$906.76	
Total per year		$5,009.00	$7,784.00	$5,009.00		$5,009.00	
Cumulative cost		$5,009.00	$7,784.00	$10,017.00	$15,568.00	$15,026.00	$23,352.00

TMR: transmyocardial laser revascularisation; MM: medical management

The resulting incremental cost of TMR compared to MM (as calculated by the secretariat) are:

- first year $17,539 – $5,009 = $12,530
- second year $711.78 – $5,009 = –$4,297 (saving)
- third year $711.78 – $5,009 = –$4,297 (saving)

In the cost analysis provided by PLC Medical Systems,[6] the cumulative costs of TMR and medical management over three years are compared, and used to demonstrate cost savings after three years. The approach is not within the concept of cost effectiveness analysis and, therefore, is considered invalid. However, if the cumulative costs become comparable at the fourth year and thereafter (at year four, $19,672 for TMR and $20,035

for medical management), it raises questions as to what might be the likely life expectancy of end-stage coronary heart disease patients and how to adjust for the savings which are likely to occur four years later. Data from the Phase II and Phase III CO_2 laser trial indicated the survival rate was 85 per cent at year one, 81 per cent at year two and 71 per cent at year three, post TMR. The survival seems likely to be about 55 per cent and 35 per cent if extrapolated to the fourth and the fifth years.

The basis of the savings claimed by the applicant is the difference in incidence of unstable angina and related hospitalisation between the two treatments. The first year's result is then extrapolated to three years after TMR, based on the assumption that the chance of having unstable angina remains unchanged in both treatment groups in the years to follow. This assumption is central to the claimed benefits of TMR, but is not discussed or justified in the application.

Incremental cost effectiveness ratios

As discussed earlier, from the second year onwards TMR results in cost savings if the response to TMR is sustained. The incremental cost effectiveness ratios calculated in the first three years following TMR are listed in Table 11.

Table 11 Incremental cost effectiveness ratios

	Year 1	Year 2	Year 3
Incremental cost of TMR	$12,530	–$4,297	–$4,297
Incremental benefits			
% free of unstable angina	69%	69%	69%
% free of disabling angina	59%	59%	59%
Incremental cost effectiveness ratio			
$/extra patient free of unstable angina	$18,159	cost savings	cost savings
$/extra patient free of disabling angina	$21,237	cost savings	cost savings

TMR: transmyocardial laser revascularisation

Sensitivity analysis

The sensitivity analysis has been conducted using the lower and the higher estimate of the 95 per cent confidence interval of the incremental benefits.

Table 12 Sensitivity analysis

Clinical benefits	Incremental cost	Incremental benefits	Incremental cost effectiveness ratio
free of unstable angina	$12,530	69%	$18,159
		lower estimate: 57.6%	$21,753
		higher estimate: 76.6%	$16,357
free of disabling angina	$12,530	59%	$21,237
		lower estimate: 41.5%	$30,192
		higher estimate: 76%	$16,487

The estimated incremental cost effectiveness ratios for the first year after TMR are:

$18,159 per extra patient free of unstable angina; and

$21,237 per extra patient free of disabling angina.[6]

Cost savings of up to $4,297 per patient per year may occur for the second year and subsequent years of follow-up, if there is sustained symptom relief.

Conclusions

Safety

TMR is associated with 3–5 per cent peri-operative mortality, and the common complications associated with any thoractomy.

Effectiveness

In both CO_2 laser RCTs,[6,7] TMR was associated with a significant reduction in the severity of angina, with 39 per cent more patients experiencing reduced angina severity by at least two classes. Consequently, consumption of anti-anginal medication was also significantly reduced. However, clinical benefits in most objective outcome measures, such as avoiding AMI, increasing exercise tolerance, and prolonging survival, were not demonstrated.

In addition, it is uncertain as to whether the effectiveness in symptom relief is sustained beyond 12 months.

Cost-effectiveness

It is considered that a cost of $21,000 for each additional patient to have angina severity decreased by two CCS classes may not be justifiable, given that the health benefits achieved at this level of expenditure are of less clinical value compared to life years saved or quality adjusted life years saved.

In addition, it should be recognised that the projected savings for the second and subsequent years, post TMR, are based on the assumption that the treatment effect is sustained and the chance of having disabling angina remains unchanged in both treatment groups. This assumption is central to the claimed cost savings of TMR, but is not substantiated by convincing evidence.

Need for further data

Further information on the long-term effectiveness and cost-effectiveness of TMR would be particularly valuable in establishing the clinical role of this technology, this may be obtained from Australian and overseas studies currently being undertaken. In addition, it would be useful to compare outcome data from the holmium laser with that from the CO_2 laser.

Recommendation

MSAC found insufficient evidence to conclude that the clinical benefits of TMR outweigh the potential risks as:

- the procedure is associated with 3–5 per cent peri-operative mortality; and
- there is uncertainty in symptom relief beyond 12 months.

In addition, the cost effectiveness ratios are considered unfavourable.

MSAC therefore recommends that public funding for TMR should not be supported at this time.

— The Minister for Health and Aged Care accepted this recommendation on 8 September 1999 —

Appendix A MSAC terms of reference and membership

The terms of reference of the Medicare Services Advisory Committee are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness; and
- references related either to new and/or existing medical technologies and procedures.

The membership of the Medicare Services Advisory Committee comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning. The members are:

Member	**Expertise**
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Ms Penny Rogers	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1/1/99)
Dr Doris Zonta	population health, representing the Australian Health Ministers' Advisory Council (until 31/12/98)

Appendix B Supporting committee

Supporting committee for MSAC application 1004
Transmyocardial laser revascularisation

Dr John Primrose (Chair) MB, BS (Hons), FRACR Senior Medical Adviser Health Access and Financing Division Department of Health and Aged Care	medical adviser to MSAC
Mr Matthew Bayfield MBBS, FRACS Cardiothoracic surgeon Royal Prince Alfred Hospital	co-opted member
Professor Terry Campbell MD, PhD, FRACP, FACC Head of Department of Medicine St Vincent's Hospital	nominated by the Royal Australasian College of Physicians
Dr John O'Sullivan MB, BS, FRACGP	nominated by the Royal Australian College of General Practitioners
Mr Peter Skillington MB, BS, B.MED.SCI, FRACS Vice President of the Australasian Society of Cardiac and Thoracic Surgeons	co-opted member
Mr Cyril Wynhdam Governing member of Consumer Health Forum	consumer representative

Abbreviations

AMI	acute myocardial infarction
AN-DRG	Australian National Diagnostic Related Group
ARDS	adult respiratory distress syndrome
CABG	coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CI	confidence interval
CHF	congestive heart failure
CVA	cerebrovascular accident
FDA	Food and Drug Administration
ICU/CCU	intensive care unit/critical care unit
MBS	Medicare Benefits Schedule
MM	medical management
MSAC	Medicare Services Advisory Committee
NHMRC	National Health and Medical Research Council
PTCA	percutaneous transluminal coronary angioplasty
TGA	Therapeutic Goods Administration
TMR	transmyocardial laser revascularisation
RCT	randomised controlled trial
SAQ	Seattle Angina Questionnaire
SF	short form

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