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Overview of synthesised literature

The efficacy and safety of cerebral bypass surgical procedures in adult patients with Moyamoya Disease

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Executive Summary

Background

The Technology Clinical Practice Committee (TCPC) is considering an application for the introduction of cerebral bypass surgery into Monash Health. The Chair, TCPC has requested for a review of literature around the safety and efficacy of cerebral bypass procedure in adult Moyamoya patients, with an aim to inform decision-making.

Objective

The review reports on the efficacy and safety of:

1) Cerebral bypass surgery as compared to conservative treatment;

2) Direct compared to indirect cerebral bypass procedures.

Methodology

A systematic search of articles in English from 2015 to 4 December 2018 was performed in three medical databases: PubMed Clinical Queries, Cochrane Database of Systematic Reviews and Ovid Medline using search terms “moyamoya” AND (“surgical treatment” OR “cerebral revascularisation”) AND “adult”. Systematic reviews, meta-analyses and randomised controlled trials reporting the safety and efficacy of cerebral bypass surgery in adult Moyamoya patients published from 2015 onwards are included. Systematic reviews and meta-analyses were assessed for quality using AMSTAR 2 [1]. An overall strength of evidence was ranked by the author (GY).

Results

Six systematic reviews/meta-analyses (of which five were of high quality) were included in the overview.

1) Four articles made comparisons between bypass procedures and conservative therapy [2-5], and

2) Four articles made comparisons between bypass methods (direct/indirect/combined) [4-7].

Quality of included studies (within the reviews/meta-analyses) was ranked at a low to moderate risk of bias by the authors. Findings from the the reviews/meta-analyses were based on a single randomised controlled trial [8], and mainly based on both prospective or retrospective cohort and case-controlled studies.

1) Cerebral bypass surgery as compared to conservative treatment (see Table A)

Evidence comparing cerebral bypass surgery to conservative therapy was scarce and at high risk of bias. Findings were drawn from a single randomised controlled trial and mainly retrospective and prospective cohort studies.

Cerebral bypass surgery reportedly reduced perioperative complications [3] and recurrent stroke rates [2,4,5] as compared to conservative therapy. To note, this significant benefit of recurrent stroke prevention was only evident in the subgroup analysis of cohort studies but not in the RCT subgroup [2].

2) Direct compared to indirect cerebral bypass procedures (see Table B)

Although perioperative complication rates between bypass surgical treatments were comparable [4-7]; there was no clear consensus to which surgical methods (direct, indirect or combined bypass) were superior in efficacy.

There was no difference in long-term ischaemia rates [7], but direct bypass resulted in lower long-term haemorrhage rates [7] and reduced risk of recurrent stroke in the adults with Moyamoya disease in two of the three reviews [4,5].

Summary of Findings

Table A. Summary of outcomes when comparing cerebral bypass and conservative therapy

Outcomes	Results	No of reviews	Quality (SR)	Quality (Studies)	Heterogeneity	Overall strength of Evidence
Safety (i.e. perioperative complications	**Favours Bypass**	**1**	**Low**	**High**	**Low**	**Low**
Efficacy (i.e., recurrent/ future stroke rate)	**Favours Bypass**	**3**	**High**	**Moderate**	**Low-high**	**Moderate**

**SR-Systematic Review or Meta-analysis*

Table B. Summary of outcomes when comparing between direct, indirect and combined bypass methods

Outcomes	Results	No of reviews	Quality (SR)	Quality (Studies)	Heterogeneity	Overall strength of Evidence
Safety (i.e. perioperative complications	**Favour Direct Bypass**	**4**	**High**	**Moderate-high**	**Low-high**	**Moderate**
Efficacy (i.e., long-term haemorrhage rate)	**Favours Direct Bypass**	**1**	**High**	**Moderate**	**High**	**Low**
Efficacy (i.e., recurrent/ future stroke rate)	**Favours Direct Bypass**	**3**	**High**	**Moderate-high**	**Moderate-high**	**Moderate**
Efficacy (i.e., long-term ischaemia rate)	**No difference**	**1**	**High**	**Moderate**	**High**	**Low**

**SR-Systematic Review or Meta-analysis*

Limitations

There was considerable heterogeneity among studies with diverse designs. Large randomised controlled studies are lacking, and therefore evidence is based only one single RCT [8], a few prospective cohort studies and mainly retrospective case studies, open to high level of bias. As a result, authors drew conclusions based on a limited number of studies with lower risk of methodological bias, or on a larger body of low level evidence with higher heterogeneity in population and study design, that was open to a higher risk of bias.

Conclusion

1) Based on limited, low levels of evidence (prospective and retrospective cohort) open to high risk of bias, the body of synthesised evidence suggests that surgical cerebral bypass (indirect or direct) may be superior compared to conservative therapy, resulting in better reduction in stroke recurrence in adult Moyamoya patients. (Table A)

2) Based on mainly low levels of evidence, with high heterogeneity in study design and patient groups, direct bypass is superior to indirect bypass in preventing long-term haemorrhage and reducing stroke recurrence, with comparable perioperative complication rates. However, no significant differences are reported in the prevention of long-term ischaemia rates between bypass patient groups. It is important to consider patient groups (whether presenting with ischaemic or haemorrhagic events) when interpreting these results. (Table B)

Full Review

Background

In surgical practice, three revascularisation strategies may be applied for the treatment of Moyamoya Disease: indirect, direct cerebral bypass, and combined revascularisation. Cerebral bypass surgery (that may involve the direct bypass of the superficial temporal artery (STA) to middle cerebral artery (MCA) bypass) for the management of adult patients with Moyamoya Disease (MMD), is being considered by the Technology Clinical Practice Committee (TCPC) for introduction into Monash Health. However, good quality evidence of the efficacy and safety of surgical cerebral bypass over conservative therapy is scarce. Moreover, there is no consensus about the best type of revascularisation surgery for the management of patients with Moyamoya Disease.

The Chair of TCPC, Prof Diana Egerton-Warburton, has requested that the Centre for Clinical Effectiveness (CCE) conduct an evidence review on the safety and efficacy of cerebral bypass procedures in adult Moyamoya patient to inform decision-making.

Objective

The two main objectives of the review are:

1) To report on the efficacy and safety of cerebral bypass (direct/indirect) surgery compared to conservative treatment;

2) To compare the efficacy and safety between the two cerebral bypass procedures (direct/indirect).

Definitions

Direct bypass included superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis. Indirect bypass include methods of incorporating well-vascularised tissue on the surface of the brain to promote angiogenesis. Combined bypasses use both direct and indirect approaches simultaneously to maximise the effect of revascularisation. Conservative or conventional therapy may include surgery i.e., evacuation of hematoma or paraventriculostomy, or medical treatment i.e., dehydration and steroid therapy. Conservative therapy is not always clearly defined in the reviews.

Methods

Table 1. Eligibility criteria

Patient	**Inclusion**: Adult patients with Moyamoya disease (MMD) **Exclusion:** Children		
Intervention	**Inclusion:** Cerebral bypass procedure (direct/indirect bypass) **Exclusion:** Other types of surgical intervention		
Comparison	**Inclusion:** Conservative therapy (medical treatment or other therapy); reviews comparing between bypass procedures		
Outcomes	**Inclusion:** Safety outcomes i.e., perioperative complications Efficacy outcomes: i.e., stroke re-occurrence, future stroke rate		
Study type	Systematic reviews, meta-analyses, randomised controlled trials	***Publication Date***	2015 onwards
		Language	English

Search Strategy

Searches of health databases were screened by one reviewer (GY), in consultation with a colleague as necessary. Search strategy and results were found in Appendix Table 8. Titles and abstracts identified were exported to EndNote X7 (Thompson, Reuters, Carlsbad, California, USA). Publications were screened using inclusion and exclusion criteria

established *a priori* (Table 1). When a screening decision could not be made based on title and abstract alone, full text was retrieved.

Assessment of Methodological Quality

Quality and risk of bias of individual studies included within the reviews will be reported as mentioned by authors of the literature selected for inclusion.

The overall quality of the systematic reviews and meta-analyses selected for inclusion in this review will be assessed by one reviewer (GY) in accordance with the eight critical domains listed in AMSTAR 2 [1], then ranked on a scale of being critically low (where the review cannot be relied on to provide an accurate and comprehensive summary of the available studies) to high quality (where the review provides an accurate and comprehensive summary of the results of the available studies that address the question). Refer to Appendix Table 9.

Ranking of Strength of Evidence

An overall strength of evidence was rated by the author (GY) taking into consideration the number, the quality of the systematic review/meta-analysis, as well as the quality and heterogeneity of their included studies. (Tables A and B)

Results

Study selection

The database search identified 122 articles.

A total of 112 articles were screened, and Reference mining of the selected articles led to one more article being identified for inclusion.

Seven articles met the inclusion criteria, however one network meta-analysis was excluded.

A total of six articles were selected for inclusion in the review.

A summary of the included studies are found in Table 2. Papers are categorised according to whether comparisons were made

a) between surgical bypass procedures (indirect/direct) and conservative treatment;

b) between direct and indirect bypass procedures, as well as between surgical bypass procedures (indirect/direct bypass) and conservative treatment;

c) between direct, combined and indirect surgical bypass procedures

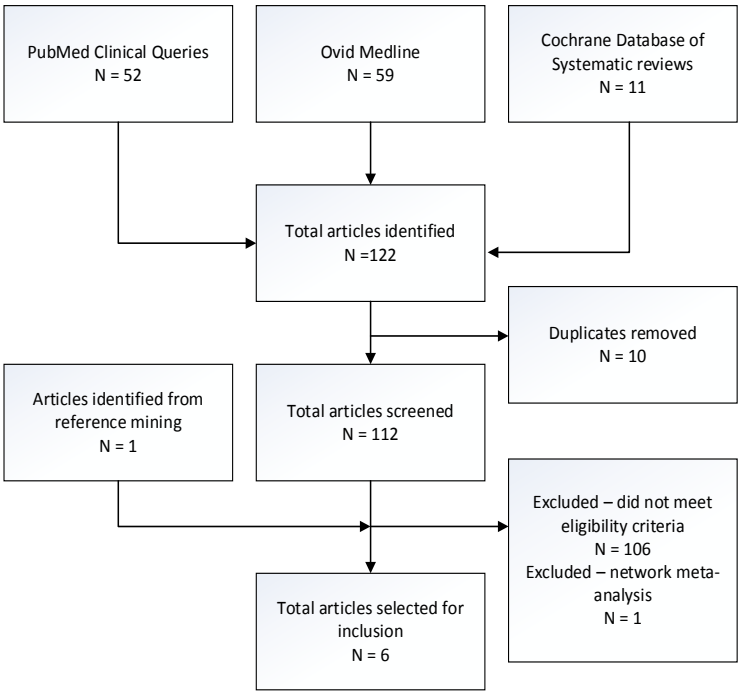

Figure 1. Search results and screening process used in the review

Characteristics of included reviews

Table 2. Characteristics of the included reviews

a) Comparison between surgical bypass procedures (indirect/direct) and conservative treatment					
Reference	**Evidence included**	**Article**	**Setting**	**Patients**	**Outcomes**
Wang *et. al.* (2017) [2] Efficacy of Surgical Treatment on the Recurrent Stroke Prevention for Adult Patients With Haemorrhagic Moyamoya Disease.	Randomised-controlled trials and retrospective cohort studies Except for blinding to participants and outcome assessment, studies were at low risk of bias.	Meta-analysis Papers n=3 Patients n=146	Japan Korea	Patients with haemorrhagic MMD Age ≥ 16 years	-Recurrent stroke rate
Liu *et. al.* (2017) [3] Safety of Extracranial–Intracranial Arterial Bypass in the Treatment of Moyamoya Disease.	Randomised controlled trials Moderate quality of evidence	Meta-analysis Papers n=2 Patients n=160	Japan	Not specified adults/children with MMD Mean age >40 years	-Perioperative complications
b) Comparisons made between direct and indirect bypass procedures, and also between surgical bypass procedures (indirect/direct) and conservative treatment					
Reference	**Evidence Included**	**Article**	**Setting**	**Patients**	**Outcomes**
Jeon *et. al.* (2018) [4] Meta-analysis of the surgical outcomes of symptomatic moyamoya disease in adults.	Randomised controlled trials, prospective controlled, and retrospective case-controlled studies Mean Newcastle-Ottawa quality score of 6.9	Meta-analysis Papers n=11 Patients n=1112	Asian Caucasian African American	Symptomatic MMD patients (ischaemic /haemorrhagic) Age >16 years	-Future stroke rate -Perioperative complications
Qian *et. al.* (2015) [5] The Efficacy of Surgical Treatment for the Secondary Prevention of Stroke in Symptomatic Moyamoya Disease A Meta-Analysis.	Randomised controlled trials, prospective controlled cohort studies and retrospective case-controlled studies Mean Newcastle-Ottawa quality score of 6.9	Meta-analysis Papers n=16 Patients n=1798	Japan Korea China Germany USA Canada	Patients with MMD Age not explicitly reported	-Recurrent stroke rate -Re-bleeding -Surgical complications
c) Comparison between direct, combined and indirect surgical bypass procedures					
Reference	**Evidence Included**	**Article**	**Setting**	**Patients**	**Outcomes**
Sun *et. al.* (2016) [6] Perioperative Complications and Long-Term Outcomes After Bypasses in Adults with Moyamoya Disease: A Systematic Review and Meta-Analysis.	Randomised controlled trials, prospective controlled, retrospective case series. Varying levels of evidence (Level 1b – Level 5)	Systematic review and meta-analysis Papers n=47; Patients n=2013	Varied countries	Patients with MMD Adults	-Perioperative haemorrhage rate -Perioperative ischaemia rate -Long term haemorrhage rate -Long term ischaemia rate
Kim *et. al.* (2016) [7] Direct Bypass Versus Indirect Bypass in Adult Moyamoya Angiopathy with Symptoms or Hemodynamic Instability: A Meta-analysis of Comparative Studies.	Comparative (retrospective and prospective cohort) studies with good methodologic quality Mean Newcastle-Ottawa quality score of 6.6	Meta-analysis Paper n=8; Patients n=536	USA, Germany Korea Japan Canada	Patients with Moyamoya angiopathy (*MMS/MMD) Adults Age >18 years	-Perioperative complication rate -Stroke incidence

**MMS – Moyamoya syndrome; MMD – Moyamoya Disease*

Syntheses of results

a) Comparison of efficacy and safety between surgical treatment (cerebral bypass) and conservative treatment

Four articles comparing surgical treatment and conservative treatment for patients with MMD report on the safety and efficacy outcomes. These are summarised according to each outcome in Tables 3 and 4 below. Only one randomised controlled trial (RCT) was identified by the authors of the meta-analyses and systematic reviews included in this overview. Therefore, results from this RCT are included in the Appendix for information.

Table 3. Perioperative complications (i.e., haemorrhage, morbidity and mortality)

Reference	No. of Studies/ Participants	Results	Heterogeneity	Quality (studies)	Publication Bias	Quality of SR
Liu et al. (2017) [3]	2 / 160	Surgical intervention resulted in less **complications** (OR [0.35], 95% CI [0.15, 0.84]).	I^2=0% Low	Moderate Low risk of bias	Not assessed due to limited no. of studies	Low-Critically flawed

Table 4. Stroke recurrence or future stroke events

Reference	No. of Studies/ Participants	Results	Heterogeneity	Quality (studies)	Publication Bias	Quality of SR
Wang et al. (2017) [2]	3 / 146	Surgical treatment showed a significant efficacy of **recurrent stroke** prevention (RR=0.44; 95% CI: 0.21–0.94; P=0.03) in the cohort study subgroup analysis of patients with haemorrhagic MMD (n=76). No significant difference of **recurrent stroke rate** was detected between surgical and conservative treatments in the subgroup analysis of the RCT subgroup ([6/42] versus [13/38]; RR=0.42; 95% CI: 0.18–0.99; P=0.05).	I^2=0%	Moderate Low risk (RCT) to high risk (cohort) of bias	Not assessed due to limited no. of studies	High
Qian et al. (2015) [5]	8 / 961	Surgical treatment significantly prevented **recurrent stroke** in haemorrhagic MMD (odds ratio (OR) of 0.17, 95% confidence interval (CI), 0.12–0.26, P<0.01)	I^2 =33%	Moderate-High Mean NOS = 6.9	None detected	High
Jeon et al. (2018) [4]	6 / 771	Bypass surgery significantly decreased the risk of **future stroke events** compared with conservative treatments in adult patients with MMD (OR 0.301, 95% CI 0.196–0.462, p<0.001).	I^2 =19%	Moderate NOS >5	None detected	High
	3 / NR	This reduction was significant in both haemorrhagic MMD patients (OR 0.319, 95% CI 0.150–0.678, p=0.003), and ischaemic MMD	I^2 =0%			
	2 / NR	patients (OR 0.240, 95% CI 0.059–0.987, p=0.048)	I^2 =68%			

**NOS – Newcastle-Ottawa Scale*

b) Comparison of efficacy and safety between direct/combined and indirect cerebral bypass procedures

Four articles comparing direct (D), indirect (I) or combined (C) bypass procedures in patients with MMD report on safety and efficacy outcomes. These are summarised according to each outcome in Tables 5 and 6 below. Unless otherwise reported, direct bypass included both direct and combined methods.

Table 5. Perioperative complications

Reference	No. of Studies/ Participants	Results	Heterogeneity	Quality (studies)	Publication Bias	Quality of SR
Sun et al. (2016) [6]	5 / 312 (I vs D) 3 / 33 (D vs C) 4 / 52 (I vs C)	No significant difference in the meta-analysis of **perioperative haemorrhage rates** and meta-analysis of **perioperative ischaemia rates** comparing between approaches (I vs D, p=0.83; D vs C, p=0.64; I vs C, p=0.62).	High	Open to high risk of bias (60% case series)	None detected or not assessed due to limited no. of studies	High
Kim et al. (2016) [7]	6 / ^NR (I vs D/C)	No significant difference in **perioperative complications** per hemisphere in adult MMD patients in the direct (or combined) bypass group as compared with the indirect bypass group (Pooled RR 1.30, 95% CI, 0.65-2.60; P = 0.46).	I^2=0%	Moderate-high Mean NOS = 6.6	None detected	High
Qian et al. (2018) [5]	11 / 1071 (I vs D/C)	No significant difference in the meta-analysis of **surgical complications** between the direct (or combined) and indirect groups (OR of 0.8, 95% CI, 0.58–1.11, P=0.18).	I^2=19%	Moderate-High Mean NOS = 6.9	None detected	High
Jeon et al. (2018) [4]	4 / 221 (I vs D/C)	No significant difference in the meta-analysis of **perioperative complications** between direct vs indirect surgery groups (OR 0.665, 95% CI 0.369–1.201, p = 0.176).	I^2=0%	Moderate NOS >5	None detected	High

*^Reported as number of events; *NOS – Newcastle-Ottawa Scale*

Table 6. Long term haemorrhage* and long term ischaemia (**i.e., intracranial haemorrhage occurring >30 days after revascularisation)*

Reference	No. of Studies/ Participants	Results	Heterogeneity	Quality (studies)	Publication Bias	Quality of SR
Sun et al. (2016) [6]	6 / 196 (I vs D)	Direct bypass conferred a significantly lower rate of **long-term haemorrhage** than did indirect bypass (OR, 0.26; 95% CI, 0.09-0.79; P = 0.02)	High	Varying levels of evidence	None detected or not assessed due limited no. of studies	High
	2 / 19 (D vs C)	No significant difference in **long-term haemorrhage rates** between direct and combined bypasses (OR, 0.91; 95% CI, 0.08-10.79; P = 0.94)	High			
	2 / 34 (I vs C)	or between indirect and combined bypasses (OR, 1.51; 95% CI, 0.21-10.77; P = 0.68).	High			
Sun et al (2016) [6]	5 / 215 (I vs D)	No significant difference in the rates of **long-term ischaemia** between direct and indirect bypasses (OR, 1.02; 95% CI, 0.40-2.57; P = 0.98)	High	Varying levels of evidence	None detected or not assessed due limited no. of studies	High
	2 / 28 (D vs C)	or between direct and combined bypasses (OR, 3.24; 95% CI, 0.23-45.51; P = 0.38)	High			
	1 / 26 (I vs C)	No significant difference in **long-term ischaemia** between indirect and combined bypass patients. (OR, 1.46; 95% CI, 0.05-39.66; P = 0.82).	High			

Table 7. Stroke recurrence and future stroke events

Reference	No. of Studies/ Participants	Results	Heterogeneity	Quality (studies)	Publication Bias	Quality of SR
Kim et al. (2016) [7]	8 / 536 (I vs D/C)	The pooled risk ratio (RR) of the **stroke incidence rate** comparing between the direct bypass group and indirect bypass group, was 0.68 (95% CI, 0.32-1.44; P=0.31). No significant differences in **recurrent stroke rate** in direct/combined bypass surgery method and the indirect bypass surgery method in adult moyamoya angiopathy patients.	I^2 =49%	Moderate-high	None detected	High
Qian et al. (2018) [5]	12 / 837 (I vs D/C)	Direct (or combined) surgery showed a significant efficacy in **recurrent stroke prevention**, (OR of 1.79, 95% CI, 1.14–2.84, P=0.01).	I^2 =28%	Moderate-High	None detected	High
Jeon et al. (2018) [4]	5 / 341 (I vs D/C)	Direct bypass was associated with a significantly lower risk of **future stroke events** (OR 0.494, 95% CI 0.264–0.927, p = 0.028)	I^2 =28%	Moderate-high	None detected	High

Discussion

Summary of evidence

Between conservative therapy and bypass surgery

Three meta-analyses compared the efficacy and safety between cerebral bypass surgery and conservative therapy. Based on a single randomised controlled trial and mainly retrospective and prospective cohort studies, surgery was reported to have significant benefit over conservative therapy in reducing perioperative complications [3], and in recurrent stroke prevention [2,3,5]. Significant efficacy of recurrent stroke prevention was only evident in the subgroup analysis of cohort studies. In the RCT subgroup, the advantage of surgical treatment was not significantly better than conservative treatment (RR=0.42; 95% CI: 0.18–0.99; P=0.05) and authors are unable to conclude that surgical treatment is more beneficial than conservative treatment in the RCT subgroup [2]. Having said this, authors of the only randomised controlled (Japanese Adult Moyamoya) trial identified by literature were also unable to declare with assurance that bypass surgery was absolutely superior to conservative therapy [8].

Findings from Liu should be interpreted with extreme caution due to the fact that the two RCTs that authors included in their analyses were from the same Japanese Adult Moyamoya (JAM) study population [3]. Although results suggest that surgical intervention may have benefits in haemorrhagic MMD patients [4,5], the meta-analysis should be interpreted with caution due to the level of heterogeneity and the fact that only one of the 11 studies included was prospective [4].

Between indirect/direct and combined bypass surgeries

Meta-analyses based on a limited number of studies demonstrate that postoperative complication rates in both direct/combined and indirect bypass surgeries are not significantly different [4-7].

Most authors report direct bypass and combined surgical therapy and compared this with indirect bypass [5-7]. One meta-analysis that included studies with mainly low level of evidence (NHMRC Level III – V) [9] showed that direct bypass was superior to indirect bypass at preventing long-term haemorrhage (OR, 0.26; 95% CI, 0.09-0.79; P=0.02) [6]. Authors conclude that direct bypass is superior to indirect bypass in reaping significant long-term favourable outcomes (i.e., improvement of functional status), in addition to lower long-term haemorrhage rates [6]. Similarly, two other meta-analyses reported significant benefits of direct bypass surgery over indirect bypass surgery [4, 5]; however one meta-analyses did not reach a statistical significance that direct or combined bypass surgery method may be more beneficial for stroke reduction in comparison with the indirect bypass surgery method [7]. Unlike the former two reviews [4, 5], analyses by Kim and colleagues were based on heterogeneous cohorts where ischaemic, haemorrhagic, and clinically asymptomatic Moyamoya patients were included [7]. As most adults present with haemorrhagic events [2], it is important to consider the cohort of MMD patients separately (i.e., whether presenting with ischaemic vs haemorrhagic attacks) when interpreting any results.

Limitations

There was considerable heterogeneity among studies with diverse designs. Large randomised controlled studies are lacking, and therefore evidence was based on a single RCT [8] (See Appendix), a few prospective cohort studies and mainly retrospective case studies, open to high level of bias. As a result, authors drew their conclusions based on a limited number of studies with lower risk of methodological bias, or on a larger body of low level evidence with higher heterogeneity in population and study design, that was open to a higher risk of bias.

Conclusions

Based on limited, low levels of evidence (prospective and retrospective cohort) open to high risk of bias, the body of synthesised evidence suggests that surgical cerebral bypass (indirect/direct) may be superior compared to conservative therapy, resulting in better reduction in stroke recurrence in adult Moyamoya patients. Based on mainly low levels of evidence, with high heterogeneity in study design, direct bypass (or in combination with indirect augmentation) is superior to indirect bypass in preventing long-term haemorrhage and reducing stroke recurrence, with no significant differences in complication rates. However, no significant differences are reported in the prevention of long-term ischaemia rates between bypass patient groups. It is important to consider patient groups (whether presenting with ischaemic or haemorrhagic events) when interpreting these results.

References

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8. Miyamoto, S., et al., Effects of extracranial-intracranial bypass for patients with hemorrhagic moyamoya disease: results of the Japan Adult Moyamoya Trial. Stroke; a journal of cerebral circulation, 2014. 45(5): p. 1415-1421.
9. National Health and Medical Research Council (NHMRC), NHMRC levels of evidence and grades for recommendations for developers of guidelines, 2009. Australian Government: NHMRC.

Appendix

Table 8. Search strategy and results

Information sources	*Date of search*	*Results*
Pubmed Clinical Queries	4 Dec 2018	52
Medline (Ovid) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1950 to Present	4 Dec 2018	59
Cochrane Database of Systematic Reviews	4 Dec 2018	11
Search Terms: “moyamoya” AND (“surgical treatment” OR “cerebral revascularisation”) AND “adult” These were based on terms used in the systematic review [Sun et al. 2016]		

Table 9. Quality rating of Systematic Reviews (critical domains in AMSTAR 2) [1]

Reference	Protocol registered	Adequacy of search	Justification of exclusion	Risk of Bias (studies)	Appropriate methods of MA	Risk of bias considered in results	Publication bias	Overall quality of SR
Wang	✔	✔	✔	✔	✔	✔	✔	**High**
Liu	✔	✔	✔	✔	✘	✔	✔	**Low**
Jeon	✔	✔	✔	✘	✔	✔	✔	**High**
Qian	✔	✔	✔	✘	✔	✔	✔	**High**
Sun	✔	✔	✔	✘	✔	✔	✔	**High**
Kim	✔	✔	✔	✘	✔	✔	✔	**High**

Overall quality was rated in accordance to AMSTAR 2 critical domains (see above), and then ranked according to the descriptions below:

High *(No or one non-critical weakness)*: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate *(More than one non-critical weakness)*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

Low *(One critical flaw with or without non-critical weaknesses):* the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

Critically low *(More than one critical flaw with or without non-critical weaknesses):* the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

Japanese Adult Moyamoya (JAM) randomised controlled trial [8]

Only one randomised controlled trial was identified by authors of the meta-analyses and systematic reviews included in this overview [8]. An excerpt of the results are described below.

Excerpt of results

- In the Japanese Adult Moyamoya (JAM) trial, Miyamoto et al. (2014) [8] compared surgical benefits of direct bypass to conservative treatment in adult MMD patients with haemorrhagic presentation in terms of primary end points (recurrent haemorrhage, completed stroke, or crescendo TIA) and secondary end points (recurrent haemorrhage, associated death, or severe morbidity). Kaplan-Meier survival analysis disclosed better outcomes for direct bypass with respect to primary and secondary end points (primary, 3.2% per year for bypass vs 8.2% per year for conservative treatment, p = 0.048; and secondary, 2.7% per year vs 7.6% per year, respectively, p = 0.042).

Table 4. Details of Outcomes and Cox Regression Analysis

	Surgical Group (n=42)		Nonsurgical Group (n=38)			
	n	Rate, %	n	Rate, %	Hazard Ratio (95% CI)	*P* Value
Primary end point	6	14.3	13	34.2	0.391 (0.148–1.029)	0.057
Recurrent bleeding	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052
Completed stroke	1	2.4	0	0.0	…	…
Crescendo TIA (bypass required)	0	0.0	1	2.6	…	…
Secondary end point (recurrent bleeding or related death/severe disability)	5	11.9	12	31.6	0.355 (0.125–1.009)	0.052

CI indicates confidence interval; and TIA transient ischemic attack.

- Authors caution the interpretation of the results of the JAM Trial, as the result was statistically marginal. Kaplan–Meier survival analysis revealed the significant benefits of bypass surgery, but the *P* values of the primary and secondary end points were 0.048 and 0.042, respectively, which are close to 0.05. In the Cox regression analysis, the upper limit of the 95% confidence interval of the hazard ratio was 1.029 for the primary end point and 1.009 for the secondary end point, both of which slightly exceed 1.0. Due to small sample size, the authors were unable to declare with assurance that bypass surgery was absolutely superior to conservative therapy.