

Effects of regional anaesthesia on mortality in patients undergoing lower extremity amputation: A retrospective pooled analysis

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ABSTRACT

Background and Aims: Lower extremity amputation (LEA) is a commonly performed surgery and is associated with significant mortality and morbidity. This review compares the impact of anaesthetic technique on 30-day mortality and other perioperative outcomes in patients undergoing LEA. **Methods:** A systematic search of databases including PubMed, Embase, Scopus and Cochrane Central Register of Controlled Trials, from January 2010 to March 2021, was performed. Studies were eligible if they compared 30-day mortality following either general anaesthesia (GA) or regional anaesthesia (RA), in adult patients undergoing LEA. **Results:** Ten retrospective observational studies were identified. Four of these studies utilised a propensity-score matching technique. Based on these four studies, RA when compared to GA, is not associated with a reduction in the 30-day mortality (Odds ratio 0.83, 95% confidence interval (CI): 0.65, 1.05, I² 20%, P = 0.12). Also there is a very low level of evidence that RA may result in a decrease in the hospital length-of-stay and intensive care unit admissions of patients undergoing LEA. **Conclusion:** RA does not decrease the 30-day postoperative mortality in patients undergoing LEA when compared to GA.

Key words: Amputation, anaesthesia, conduction, lower extremity

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INTRODUCTION

The leading indication for lower extremity amputation (LEA) in the United States is peripheral vascular disease, primarily in the older person with diabetes mellitus complicated by peripheral neuropathy, ulcers, gangrene or osteomyelitis.^[1] Generally, these patients are at a high-risk for poor postoperative outcomes because of their old age, sepsis and multiple medical comorbidities (such as ischaemic heart disease, renal impairment and stroke).^[2] Consequently, LEA has been associated with 30-day postoperative mortality rates that are as high as 7-32%.^[3,4]

In theory, regional anaesthesia (RA) may confer some advantages over general anaesthesia (GA). For example, RA may result in less hypotension, bleeding, venous thromboembolism, surgical stress

and pulmonary complications.^[5] For this reason, in the recent years, a number of studies have examined whether RA is associated with lower 30-day postoperative mortality when compared to GA for patients undergoing LEA.

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This pooled analysis was performed to determine if RA reduces the 30-day mortality of patients undergoing LEA surgery, when compared to GA.

METHODS

This review followed the recommendations outlined in the Cochrane handbook for systematic reviews and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.^[6,7] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42021231265).

Search strategy

An electronic search was conducted using the following databases from January 2010 to August 2021: PubMed, Embase, Scopus and Cochrane Central Register of Controlled Trials. No language restrictions were applied. All publications including conference abstracts were included in the initial search. The search used key terms such as “anesthesia”, “lower extremity” and “amputation”. The details of the search strategy are available in the Appendix 1. The reference lists of all included studies were manually searched to identify other studies which were eligible for inclusion.

Two reviewers (NP and SQ) independently reviewed the titles and abstracts of all search entries to exclude irrelevant studies. The full text of the remaining studies was further examined for inclusion based on the inclusion and exclusion criteria. Disagreements about the study eligibility were arbitrated by another author (CL).

Selection criteria

The inclusion criteria were studies involving:

- Population: adult patients (>18 years old) undergoing non-traumatic LEA
- Intervention: RA (central neuraxial and/or peripheral nerve block)
- Comparator: GA
- Outcome (primary): 30-day mortality

Studies that involved any ongoing trials, children, animals, combined GA/RA technique and LEA for trauma/malignancy were excluded.

Quality assessment

Two reviewers (NP, SQ) independently assessed the quality of each included study. The Newcastle-Ottawa

Scale (NOS),^[8] an instrument for assessing the quality of non-randomised studies, was used to assess for bias. This scale contains eight items within three domains (selection, comparability and outcomes). NOS scores of 7-9, 4-6 and 0-3 indicate that the studies are of high quality, high risk of bias and very high risk of bias, respectively.^[8] The level of evidence was assessed in accordance to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.^[9] As all of the included studies were retrospective in nature, the evidence for each outcome was initially graded as low. The grade was then upgraded or downgraded based on the risk of bias, imprecision, inconsistency, indirectness and publication bias. Any disagreement was resolved through consultation with another author (CL). The NOS and GRADE tables may be found in the Appendix 2 and 3.

Data extraction

Two reviewers (NP, SQ) independently extracted data into a standardised template created using Microsoft Excel version 2016 (Redmond: Microsoft Corporation, 2015). The following data was collected from each study: author names, publication year, study design, sample size, characteristics of study participants, type of intervention, 30-day mortality, 90-day mortality, intensive care unit (ICU) admission, length of stay, cardiovascular outcomes, respiratory outcomes, stroke, renal failure, vasopressor use, wound complications, bleeding and blood transfusion. Any disagreements were resolved through consultation with another reviewer (CL).

Data analysis

Statistical analyses were performed using the Review Manager (RevMan) software version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R Studio software Version 1.2.1335 (Boston: R Studio Inc, 2018). Only studies that utilised propensity-score matched outcomes were pooled. Continuous data were compared using mean differences and 95% confidence intervals (CIs). If studies reported the variables in median and interquartile range, the Box-Cox method was used to estimate the sample mean and standard variance.^[10] Dichotomous data were pooled and analysed using the Mantel-Haenszel odds ratio with 95% CIs. Random effects model was applied to all pooled data. The Higgin's I² test was used to estimate the degree of statistical heterogeneity. I² of <40%, 30-50%, 50-75% and 75-100% were considered to represent non-important,

moderate, substantial and considerable heterogeneity, respectively.^[6] Funnel plots for the primary outcome were constructed and visually inspected to evaluate for the risk of publication bias.

RESULTS

Study selection and characteristics

A total of 1082 studies were identified during the initial search. After the removal of 435 duplicate studies, 649 titles and abstracts were screened. Thirty-two studies were identified for full-text review, of which 19 studies were excluded as they did not fulfil the inclusion criteria. Another three studies were excluded because their study population were derived from the same National Surgical Quality Improvement Program database. To avoid double-counting, the study with the larger sample size was used. Ten studies were included in the review [Figure 1].

All of the studies that were included in this review were retrospective observational studies that examined the impact of anaesthetic technique on 30-day mortality and perioperative outcomes in adult patients undergoing LEA. These studies were conducted between 2013 and 2018. Eight studies were restricted to patients undergoing major LEA, while two studies involved patients undergoing major and minor LEA. Six studies compared GA with either peripheral nerve blocks or central neuraxial anaesthesia. Three studies compared GA with central neuraxial anaesthesia alone, and one study compared GA with peripheral nerve blocks alone. Eight out of 10 studies were assessed to be of high quality on the NOS [Table 1].

1. 30-day Mortality after LEA

The overall incidence (GA and RA groups) of 30-day mortality following LEA ranged from 3.7% to

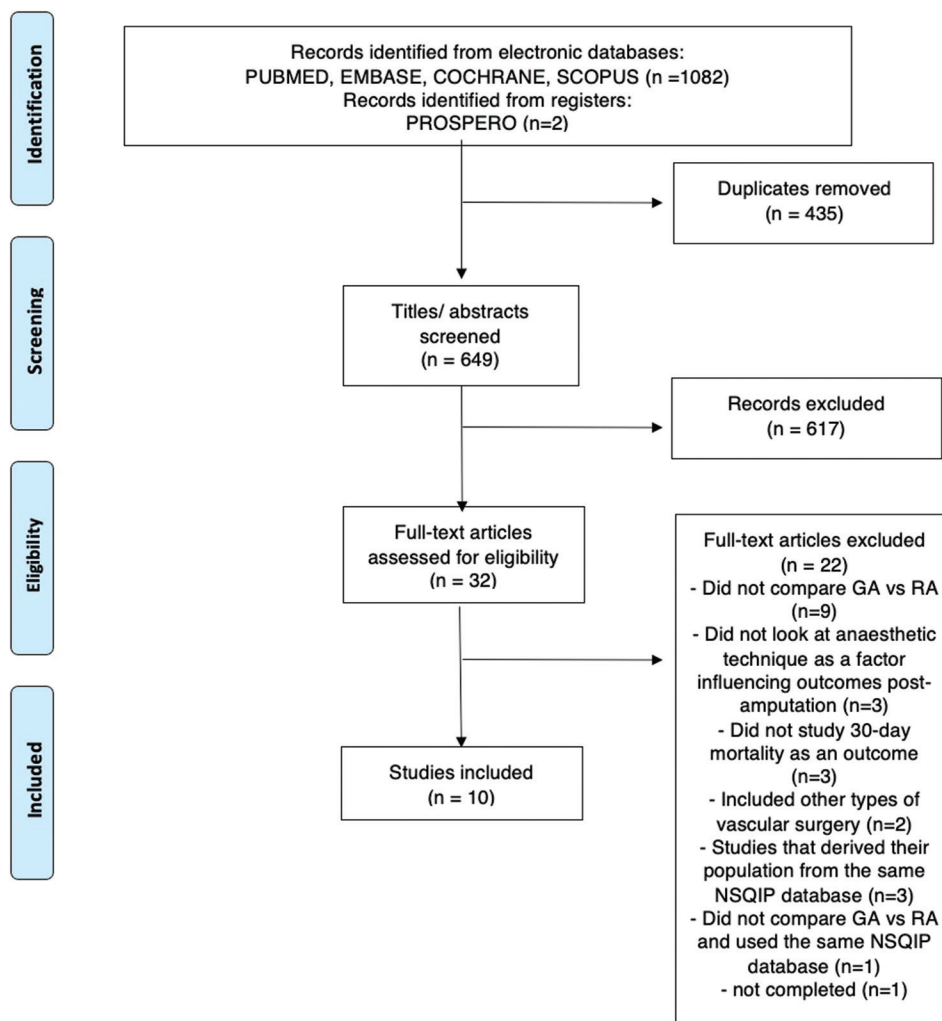


Figure 1: PRISMA flow diagram. NSQIP: National Surgical Quality Improvement Program; GA: General anaesthesia; RA: Regional anaesthesia; vs: versus; n: Number

15%.^[11,12] Out of the 10 studies, two did not control for confounders.^[13,14] The rest of the studies utilised either multivariate logistic regression^[12,15-17] or propensity score matching^[4,11,18,19] to adjust for confounders. With the exception of one study which was reported by SA Khan *et al.*,^[4] all of the eight studies that controlled for confounders reported no significant benefit of RA over GA in reducing the incidence of 30-day mortality after LEA [Table 2].

A meta-analysis was performed using the results of the four studies^[4,11,18,19] which utilised propensity score matching. A funnel plot constructed to investigate publication bias showed a symmetrical distribution [Figure 2] and no important heterogeneity was observed

among the studies. Based on these four studies which involved 6647 patients (of whom, 1933 received RA), the use of RA did not result in a significant reduction in incidence of 30-day mortality following LEA (odds ratio (OR) 0.83, 95% CI: 0.65, 1.05, I² 20%, P = 0.12) [Figure 3]. This evidence was graded as low.

It was postulated that the impact of RA may be greater in patients undergoing major LEA (defined as amputation above the ankle joint^[20]) as major LEA is associated with higher mortality rates when compared to minor LEA.^[21] As such, a subgroup analysis was performed with studies that looked only at patients undergoing major LEA. Two studies^[4,18] involving 2570 patients (of whom, 1015 received RA)

Table 1: Characteristics of studies

Authors and Year of Study	Design	Sample size	Surgery	Intervention	Comparison
H. Abe <i>et al.</i> , 2020*	Retrospective cohort study	11796	Below knee amputation (BKA) or foot amputation	Peripheral nerve block (PNB)	General anaesthesia (GA)
J. Dittman <i>et al.</i> , 2020	Retrospective cohort study	20,879	Above knee amputation (AKA)	PNB or central neuraxial block	GA
J Dittman. <i>et al.</i> , 2020	Retrospective cohort study	27709	BKA	PNB or central neuraxial block	GA
M. R. Hall <i>et al.</i> , 2020	Retrospective cohort study	5567	Elective major lower extremity amputation (LEA)	PNB or central neuraxial block	GA
S. J. Kim <i>et al.</i> , 2019*	Retrospective cohort study	519	Major or minor LEA secondary to diabetic foot or peripheral vascular disease	PNB or spinal anaesthesia	GA
M. Niskakangas <i>et al.</i> , 2018	Retrospective cohort study	323	Major LEA secondary to peripheral vascular disease	Spinal anaesthesia	GA
B. Bilgili <i>et al.</i> , 2017	Retrospective cohort study	441	Major LEA	Spinal or combined spinal epidural anaesthesia	GA
C. C. Moreira <i>et al.</i> , 2016*	Retrospective cohort study	3260	Major LEA	PNB or spinal anaesthesia	GA
J. Chery <i>et al.</i> , 2014	Retrospective cohort study	407	Major LEA	Spinal or combined spinal epidural anaesthesia	GA
S. A. Khan <i>et al.</i> , 2013*	Retrospective cohort study	1365	Major LEA	PNB or central neuraxial block	GA

* Studies utilised propensity-score matching to balance confounders

Table 2: Primary outcome (30-day mortality)

Authors and Year of Study	Mortality (RA)%	Mortality (GA)%	30-day mortality OR (95% CI) Rate	P	Note
H. Abe <i>et al.</i> , 2020*	4.6	4.1	1.11 (0.75, 1.64),	0.60	-
J. Dittman <i>et al.</i> , 2020	16.3	14.6	-	0.003	Conference abstract
J Dittman. <i>et al.</i> , 2020	-	-	-	-	Conference abstract
M. R. Hall <i>et al.</i> , 2020	6.8	5.8	1.03 (0.9, 1.17)	0.3	-
S. J. Kim <i>et al.</i> , 2019 *	2.9	3.5	0.83 (0.28, 2.46)	0.737	-
M. Niskakangas <i>et al.</i> , 2018	7	11	7% in RA group vs 11% in GA group	0.16	-
B. Bilgili <i>et al.</i> , 2017	8.3	14.4	8.3% in RA group vs 14.4% in GA group	0.134	-
C. C. Moreira <i>et al.</i> , 2016 *	11.7	14.4	1.27 (0.93, 1.73)	0.136	-
J. Chery <i>et al.</i> , 2014	10	13	1.43 (0.75, 2.7)	0.27	-
S. A. Khan <i>et al.</i> , 2013 *	9.3	13.6	Total matched population: 1.5 (1.0, 2.3)	0.04	-

*propensity-matched study, RA – regional anaesthesia, GA – general anaesthesia, OR – odds ratio, CI – Confidence interval; vs – versus.

were included in this subgroup meta-analysis which found that RA significantly reduced 30-day mortality compared to GA (OR 0.73; 95% CI (0.57, 0.94), I² 0%, P = 0.01). See Figure 3 (forest plot).

2. 90-day Mortality after LEA

90-day mortality was reported in two propensity-matched studies.^[4,11] Individually, neither study found a significant difference in the 90-day mortality with the use of either RA or GA. A meta-analysis including the two studies also showed no difference in the 90-day mortality with the use of RA (OR 0.78; 95% CI (0.57,1.07), I² 0%, P = 0.13) [Figure 4]. This evidence was graded as low. A summary of all relevant secondary outcomes, including 90-day mortality, may be found in Table 3.

3. Hospital length of stay

Six studies^[4,12-15,17] reported the length of hospital stay (H-LOS). There is some evidence that H-LOS is

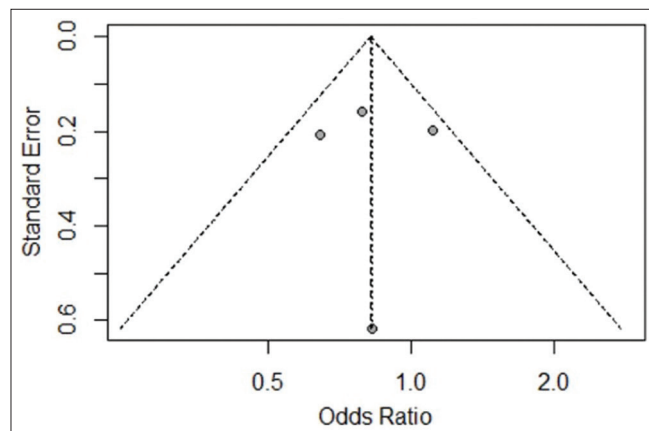


Figure 2: Funnel plot – 30-day mortality rate, regional anaesthesia versus general anaesthesia (primary outcome)

shorter in patients who received RA compared to GA. Three studies^[13-15] reported a statistically significant shorter H-LOS with the use of RA with mean differences ranging between 3.7 to 5 days.^[13,15]

4. Intensive care unit admission

There is limited evidence that RA is associated with reduced ICU admission. The admission rate to ICU following LEA was about 8%.^[14] Two studies reported ICU admission as an outcome measure. Both these studies reported a significantly lower ICU admission (by 52.1%^[11] and 84%^[13]) in the RA group compared to the GA group. Among the patients who were admitted to the ICU, RA and GA were associated with similar durations of ICU stay.^[11,14]

5. Cardiac outcomes

Cardiac outcomes appear to be similar between the RA and GA groups. Six^[11,13-16,22] out of seven^[11-16,22] studies reported no differences in the incidences of myocardial infarction between the RA and GA groups. A study by Dittman *et al.* found a small but statistical increase in the incidence of myocardial infarction in patients who received RA for above-knee amputation.^[12] The reason for this is unclear and may represent a chance error. Two further studies^[17,18] examined composite cardiac outcomes and were unable to detect a statistically significant benefit of RA over GA.

6. Pulmonary outcomes

There is evidence that RA does not result in reduced incidences of pneumonia,^[11,13-15,18,22] pulmonary embolism,^[12,13,15,16] prolonged ventilation,^[11,3,15,19] hypoxia^[11] and unplanned intubation.^[11,19] A study

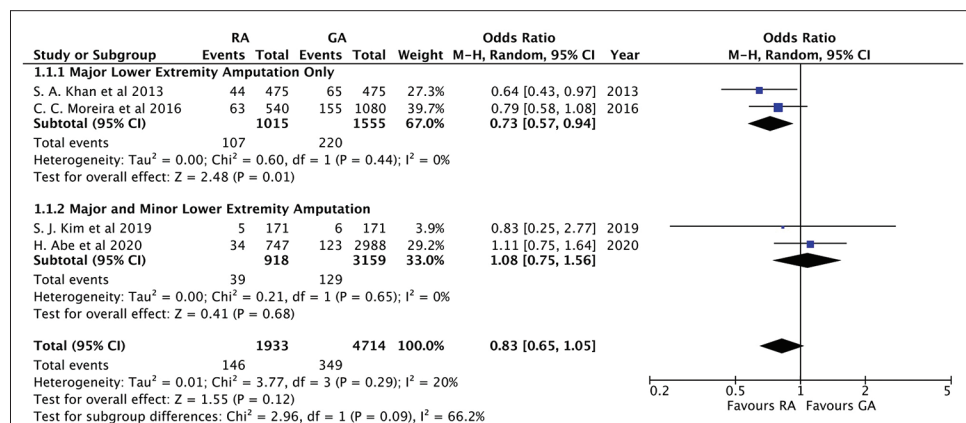


Figure 3: Forest plot –30-day mortality rate, RA versus GA (primary outcome). CI: Confidence interval; RA:Regional anaesthesia; GA:General anaesthesia

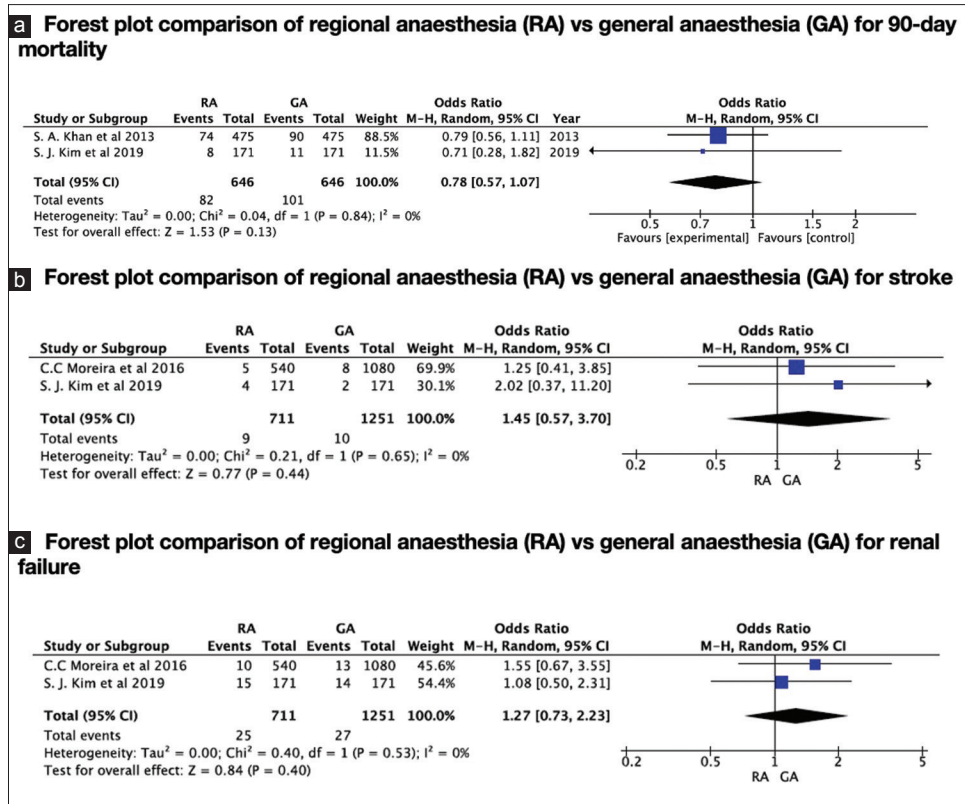


Figure 4: Forest plot – secondary outcome measures, regional anaesthesia vs general anaesthesia; (a) 90-day mortality, (b) Stroke, (c) Renal failure. vs: versus

utilising a composite pulmonary outcome yielded similar results.^[18]

7. Neurological outcomes

There is evidence that RA does not result in increase in cerebrovascular accidents. Five studies reported no association between the choice of anaesthesia and cerebrovascular accidents.^[11,12,16,18,22] A meta-analysis performed on two propensity-matched studies^[11,18] involving a total of 1,962 patients showed that RA and GA were associated with similar incidences of cerebrovascular accidents. (OR 1.45; 95% CI (0.57, 3.70), I² 0%, P = 0.44) [Figure 4]. This evidence was graded as very low.

8. Renal outcomes

There is very low evidence that RA does not reduce renal failure. Five studies examined the association between RA and renal failure.^[11,12,15,16,18] None of them found an association between RA and decrease in incidence of renal failure. A meta-analysis of two propensity-matched studies^[11,18] showed that RA and GA were associated with similar incidences of renal failure (OR 1.27; 95%CI (0.73, 2.23), I² 0%, P = 0.4) [Figure 4]. This evidence was graded as low.

9. Blood loss and blood transfusion

Five studies^[11-13,15,16] reported blood transfusion and one reported blood loss.^[15] None of these studies show a difference between the RA and GA groups.

DISCUSSION

Consistent with the published literature, this study found that LEA is associated with a high mortality.^[23] The main finding of this study is that RA, when compared to GA, does not appear to reduce the incidence of 30-day and 90-day mortality following LEA. However, one study pointed out that in the high risk patients, there might be a benefit of RA over GA in terms of reducing the 30-day mortality.^[4]

There is also evidence that RA is not associated with reduced cardiac, neurological, renal and bleeding complications after LEA. However, some studies have found that RA is associated with a lower H-LOS and ICU admission rate. But since these studies were not designed to assess H-LOS and ICU admission rates, these findings should be considered exploratory rather than definitive. Further studies are required to understand the impact of RA on H-LOS and ICU admission.

Table 3: Secondary outcomes	
Authors (Year)	Reported Outcomes [†] (OR (95% CI))
90-day mortality	
S. J. Kim <i>et al.</i> , 2019	0.72 (0.3, 1.75), <i>P</i> =0.47
S. A. Khan <i>et al.</i> , 2013	Total matched population: 1.3 (0.9, 1.8), <i>P</i> =0.19
Hospital length of stay	
M. R. Hall <i>et al.</i> , 2020	8.35 (0, 24.5) in RA group vs 8.5 (0, 43.5) in GA group, <i>P</i> =0.15
S. J. Kim <i>et al.</i> , 2019	10 [6-15] in RA group vs 10 [6-19] in GA group, <i>P</i> =0.24
M. Niskakangas <i>et al.</i> , 2018	5 [3-7] in RA group vs 5 [3-11] in GA group, <i>P</i> =0.02
B. Bilgili <i>et al.</i> , 2017	13.3 (13, 13.6) in RA group vs 18.29 (17.8, 18.8) in GA group, <i>P</i> =0.001
J. Chery <i>et al.</i> , 2014	19.4 (17.4, 21.4) in RA group vs 23.1 (20.2, 26) in GA group, <i>P</i> =0.04
S. A. Khan <i>et al.</i> , 2013	23 [16-38] in RA group vs 24 [14-35] in GA group, <i>P</i> >0.05
Intensive care unit admission	
S. J. Kim <i>et al.</i> , 2019	OR 0.46 (0.23, 0.94), <i>P</i> =0.032
M. Niskakangas <i>et al.</i> , 2018	4% in RA group vs 25% in GA group, <i>P</i> <0.001
Cardiac outcomes	
H. Abe <i>et al.</i> , 2020	Composite cardiac outcomes [‡] OR 0.91 (0.5, 1.66), <i>P</i> =0.756
J. Dittman <i>et al.</i> , 2020	MI: 1.4% in RA group vs 0.9% in GA group, <i>P</i> =0.003
M. R. Hall <i>et al.</i> , 2020	MACE [§] : OR 0.94 (0.72, 1.23), <i>P</i> =0.37
S. J. Kim <i>et al.</i> , 2019	MI: OR 1.25 (0.34, 4.65), <i>P</i> =0.739 Cardiac arrest: OR 3.5 (0.73, 16.8), <i>P</i> =0.118 Hypotension: OR 0.10 (0.05, 0.20), <i>P</i> <0.001 Vasopressor use: OR 0.145 (0.07, 0.27), <i>P</i> <0.001
M. Niskakangas <i>et al.</i> , 2018	MI: 4% in RA group vs 9% GA group <i>P</i> =0.16
B. Bilgili <i>et al.</i> , 2017	MI: 15.3% in RA group vs 20.6% in GA group, <i>P</i> =0.284 Arrhythmia: 16.7% in RA group vs 23.7% in GA group, <i>P</i> =0.176
C. C. Moreira <i>et al.</i> , 2016	MI/cardiac arrest: OR 0.91 (0.50, 1.66), <i>P</i> =0.756
J. Chery <i>et al.</i> , 2014	MI: OR 0.82 (0.37, 1.68), <i>P</i> =0.59 Arrhythmia: OR 2.15 (1.28, 3.62), <i>P</i> =0.004
Pulmonary outcomes	
S. J. Kim <i>et al.</i> , 2019	Pneumonia: OR 0.58 (0.23, 1.48), <i>P</i> =0.257 Ventilator support: OR 1.17 (0.39, 3.47), <i>P</i> =0.78
M. Niskakangas <i>et al.</i> , 2018	Pneumonia: 7% in RA group vs 12% in GA group, <i>P</i> =0.11
B. Bilgili <i>et al.</i> , 2017	Pneumonia: 11.8% in RA group vs 7.2% in GA group, <i>P</i> =0.34 Ventilator support: 11.1% in RA group vs 11.3% in GA group, <i>P</i> =1.00 Pulmonary embolism: 1.4% in RA group vs 4.1% in GA group, <i>P</i> =0.22

Contd...

Table 3: Contd...	
Authors (Year)	Reported Outcomes [†] (OR (95% CI))
C. C. Moreira <i>et al.</i> , 2016	Composite pulmonary outcomes: OR 1.1 (0.73, 1.66), <i>P</i> =0.63
J. Chery <i>et al.</i> , 2014	Composite pulmonary outcomes: OR 1.92 (1.14, 3.24), <i>P</i> =0.01 Pneumonia: OR 1.52 (0.79, 2.9), <i>P</i> =0.2 Pulmonary embolism: OR 2.29 (0.49, 11.82), <i>P</i> =0.29 Ventilator support: OR 2.22 (1.18, 4.22), <i>P</i> =0.01
Neurological outcomes	
H. Abe <i>et al.</i> , 2020	Delirium: OR 0.75 (0.57, 0.98), <i>P</i> =0.04
S. J. Kim <i>et al.</i> , 2019	CVA: OR 2 (0.37, 10.9), <i>P</i> =0.42
C. C. Moreira <i>et al.</i> , 2016	CVA: OR 0.80 (0.26, 2.45), <i>P</i> =0.694
J. Chery <i>et al.</i> , 2014	CVA: OR 0.98 (0.42, 2.15), <i>P</i> =0.96
Renal outcomes	
S. J. Kim <i>et al.</i> , 2019	OR 1.08 (0.49, 2.37), <i>P</i> =0.84
C. C. Moreira <i>et al.</i> , 2016	OR 0.65 (0.28, 1.48), <i>P</i> =0.30
J. Chery <i>et al.</i> , 2014	OR 1.65 (0.98, 2.77), <i>P</i> =0.06
BL and BT	
J. Dittman <i>et al.</i> , 2020	BL: 0.2% in RA group vs 0.5% in GA group, <i>P</i> =0.0003
S. J. Kim <i>et al.</i> , 2019	BT: OR 0.5 (0.23, 1.11), <i>P</i> =0.089
B. Bilgili <i>et al.</i> , 2017	BT: 0.4% in RA group vs 22.7% in GA group, <i>P</i> =0.016
J. Chery <i>et al.</i> , 2014	BT: 1.33 ml/kg in RA group vs 1.872 ml/kg in GA group, <i>P</i> =0.03 BL: 156 ml in RA group vs 154 ml in GA group, <i>P</i> =0.86

GA – general anaesthesia, RA – regional anaesthesia, CVA – cerebrovascular accident, MI – myocardial infarction, MACE – Major adverse cardiac events, BL – blood loss, BT – blood transfusion, CI – confidence interval, OR – odds ratio. [†]Continuous data as mean +/- standard deviation or mean (95% CI) or median [interquartile range]. [‡]Composite morbidity was defined as the occurrence of any life-threatening complication (acute coronary syndrome, stroke, or those indicated by cardio-pulmonary resuscitation, unplanned intubation, cardioversion, defibrillation, continuous haemodiafiltration over 30 days or prolonged postoperative mechanical ventilation lasting more than 7 days after lower extremity amputation. [§]MACE was defined as a composite of postoperative myocardial infarction, persistent and clinically significant arrhythmia requiring treatment and new onset/worsened congestive cardiac failure.

The strength of this study is that, it is the first review that has examined this clinical question. The studies included in this review had large sample sizes and looked at an objective outcome measure. Most of the studies scored well on the NOS, an instrument to assess the risk of bias in non-randomised trials. Across most of the outcome measures, the results were fairly homogenous. Although this review included only observational studies, the role of observational studies should not be downplayed when studying a harmful outcome. Randomised controlled trials, while useful for the examination of efficacy, may not be as useful

for determining the rates of adverse events. This is due to the low frequency of events, small number of participants, restrictive inclusion/exclusion criteria and short follow-up periods.^[24] Furthermore, it is considered unethical to randomise patients to a study that is evaluating a harmful outcome.^[25] In this context, this review presents the best level of evidence till date on this topic.

The major limitation of this review is that while many studies adjusted for confounders, not all utilised a propensity score-matching technique. Hence, some of the studies were not pooled in the meta-analysis. Moreover, the results of secondary outcomes such as 90-day mortality, H-LOS and ICU admission should be interpreted with caution. Nevertheless, the results from these papers appear to have fairly uniform results in the primary and secondary outcome measures. This strengthens our confidence that the assessment is accurate. Another limitation is that most studies reported both peripheral and central neuraxial anaesthesia as RA. Since, peripheral nerve blocks result in less physiological derangement than central neuraxial anaesthesia, future studies that compare peripheral nerve blocks to GA may possibly give rise to opposing results from this review.^[26,27]

Taken together, during the informed consent process, patients should not be routinely counselled that RA reduces the risk of mortality. The choice of the anaesthesia technique should be individualised based on factors such as patient comorbidities, presence of a bleeding diathesis, haemodynamic stability, patient preference etc. It is nevertheless, still reasonable to offer RA to reduce the risk of ICU admission, reduce opioid consumption, reduce pain scores and prevent chronic pain.^[11,14,28]

CONCLUSION

LEA is a commonly performed surgery that carries significant mortality and morbidity. In this study, RA was not found to reduce the 30-day mortality after LEA when compared to GA. There is very low level of evidence that RA may decrease hospital length of stay and ICU admission rates

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX 1: SEARCH STRATEGY

Document full search strategies as run in each database adhering to PRISMA-S checklist.

Database: Medline (PubMed)

Date of Search: 19 Jan 2022

Number of Results: 221

Limits applied (refer to PRISMA-S item 9): Jan 2010- Aug 2021

Filters applied (refer to PRISMA-S item 10): none

Search Strategy (copy and paste as run)

("anesthesia"[MeSH Terms] OR ("anesthetics"[MeSH Terms] OR "anesthesiology"[MeSH Terms]) OR "anaesthe*"[Title/Abstract] OR "anesthe*"[Title/Abstract]) AND ("lower extremity"[MeSH Terms] OR "lower"[Title/Abstract] OR "leg"[Title/Abstract] OR "knee"[Title/Abstract]) AND ("Amputation"[MeSH Terms] OR "Amputation"[Title/Abstract]) AND (2010/1/1:2021/8/31[pdat])

Database: Embase.com

Date of Search: 19 Jan 2022

Number of Results: 482

Limits applied (refer to PRISMA-S item 9): Jan 2010- Aug 2021

Filters applied (refer to PRISMA-S item 10): none

Search Strategy (copy and paste as run)

('anesthesia/exp OR 'anesthetic agent'/exp OR anaesthe*:ti, ab OR anesthe*:ti, ab) AND ('leg amputation'/exp OR ((lower OR leg OR knee) NEAR/3 amputation):ti, ab)) AND [01-01-2010]/sd NOT [01-09-2021]/sd

Database: Scopus

Date of Search: 19 Jan 2022

Number of Results: 310

Limits applied (refer to PRISMA-S item 9): Jan 2010- Aug 2021

Filters applied (refer to PRISMA-S item 10): none

Search Strategy (copy and paste as run)

TITLE-ABS-KEY (((anaesthe* OR anesthe*) AND ((lower OR leg OR knee) W/3 amputation))) AND PUBYEAR>2009 AND PUBYEAR<2022

Database: Cochrane Central Register of Controlled Trials

Date of Search: 19 Jan 2022

Number of Results: 69

Limits applied (refer to PRISMA-S item 9): Jan 2010- Aug 2021

Filters applied (refer to PRISMA-S item 10): none

Search Strategy (copy and paste as run)

#1 MeSH descriptor: [Anesthesia] explode all trees	20225
#2 MeSH descriptor: [Anesthetics] explode all trees	16637
#3 (anaesthe* OR anesthe*):ti, ab, kw	90592
#4 MeSH descriptor: [Lower Extremity] explode all trees	7573
#5 MeSH descriptor: [Amputation] explode all trees	478
#6 ((lower OR leg OR knee) NEAR/3 amputation):ti, ab, kw	762
#7 (#1 OR #2 OR #3) AND ((#4 AND #5) OR #6)	70
#8 01/01/2010 – 31/08/2021	69

APPENDIX 2 - NEWCASTLE-OTTAWA SCALE (NOS) FOR ASSESSMENT OF QUALITY OF INCLUDED STUDIES

Study Author, year	Selection			Comparability		Outcome		Score	
	RA group representative of the average patient undergoing LEA	GA group drawn from the same community as the intervention cohort	Secure record (eg healthcare record) or structured interview	Outcome not present at start of study	Study controls age and at least two comorbidities	Study controls for any two additional risk factors	Confirmation of 30-day mortality by reference to secure records		Follow-up >1 month
H. Abe <i>et al.</i> , 2020	★	★	★	★	★	★	-	★	★
J. Dittman <i>et al.</i> , 2020	★	★	★	★	★	★	-	★	-
J Dittman. <i>et al.</i> , 2020	★	★	★	★	★	★	-	★	-
M. R. Hall <i>et al.</i> , 2020	★	★	★	★	★	★	★	★	★
S. J. Kim <i>et al.</i> , 2019	★	★	★	★	★	★	-	★	-
M. Niskakangas <i>et al.</i> , 2018	★	★	★	★	-	-	-	★	★
B. Bilgili <i>et al.</i> , 2017	★	★	★	★	-	-	★	★	★
C. C. Moreira <i>et al.</i> , 2016	★	★	★	★	★	★	★	★	-
J. Chery <i>et al.</i> , 2014	★	★	★	★	★	★	-	★	★
S. A. Khan <i>et al.</i> , 2013	★	★	★	★	★	★	★	★	-

GA – general anaesthesia, RA – regional anaesthesia, LEA – lower extremity amputation

APPENDIX 3: SUMMARY OF FINDINGS TABLE
Question: RA compared to GA for Lower extremity amputation

№ of studies	Study design	Certainty assessment				№ of patients		Effect Absolute (95% CI)	Relative (95% CI)	Certainty Importance	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA				GA
4	observational studies	not serious	not serious	not serious	not serious	none	146/1933 (7.6%)	349/4714 (7.4%)	OR 0.83 (0.65 to 1.05)	12 fewer per 1,000 (from 25 fewer to 3 more) Low	⊕⊕○○○ Critical
2	observational studies	not serious	not serious	not serious	not serious	none	82/656 (12.5%)	101/646 (15.6%)	OR 0.78 (0.57 to 1.07)	30 fewer per 1,000 (from 61 fewer to 9 more) Low	⊕⊕○○○ Important
2	observational studies	not serious	not serious	not serious	serious ^a	none	9/711 (1.3%)	10/1251 (0.8%)	OR 1.45 (0.57 to 3.70)	4 more per 1,000 (from 3 fewer to 21 more) Very low	⊕○○○○ Important
2	observational studies	not serious	not serious	not serious	not serious	none	25/711 (3.5%)	27/1251 (2.2%)	OR 1.27 (0.73 to 2.23)	6 more per 1,000 (from 6 fewer to 25 more) Low	⊕⊕○○○ Important

GA: general anaesthesia; RA: regional anaesthesia CI: confidence interval; OR: odds ratio