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## REVIEW ARTICLE

# Effectiveness of combined regional-general anesthesia for reducing mortality in coronary artery bypass: meta-analysis<sup>☆</sup>



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### KEYWORDS

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### Abstract

**Background and objectives:** Neuraxial anesthesia (NA) has been used in association with general anesthesia (GA) for coronary artery bypass; however, anticoagulation during surgery makes us question the viability of benefits by the risk of epidural hematoma. The aim of this study was to perform a meta-analysis examining the efficacy of NA associated with GA compared to GA alone for coronary artery bypass on mortality reduction.

**Methods:** Mortality, arrhythmias, cerebrovascular accident (CVA), myocardial infarction (MI), length of hospital stay (LHS), length of ICU stay (ICUS), reoperations, blood transfusion (BT), quality of life, satisfaction degree, and postoperative cognitive dysfunction were analyzed. The weighted mean difference (MD) was estimated for continuous variables, and relative risk (RR) and risk difference (RD) for categorical variables.

**Results:** 17 original articles analyzed. Meta-analysis of mortality (RD = -0.01, 95% CI = -0.03 to 0.01), CVA (RR = 0.79, 95% CI = 0.32–1.95), MI (RR = 0.96, 95% CI = 0.52–1.79) and LHS (MD = -1.94, 95% CI = -3.99 to 0.12) were not statistically significant. Arrhythmia was less frequent with NA (RR = 0.68, 95% CI = 0.50–0.93). ICUS was lower in NA (MD = -2.09, 95% CI = -2.92 to -1.26).

**Conclusion:** There was no significant difference in mortality. Combined NA and GA showed lower incidence of arrhythmias and lower ICUS.

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**PALAVRAS-CHAVE**

Anestesia geral;  
Anestesia neuroaxial;  
Mortalidade;  
Metanálise;  
Revascularização  
miocárdica

## Efetividade da associação da anestesia regional à anestesia geral na redução da mortalidade em revascularização miocárdica: metanálise

**Resumo**

**Introdução e objetivos:** A anestesia neuroaxial (AN) vem sendo utilizada em associação com a anestesia geral (AG) para revascularização miocárdica, entretanto a anticoagulação durante a cirurgia torna questionável a viabilidade dos benefícios mediante o risco de hematoma de espaço peridural. O objetivo deste estudo foi executar metanálises analisando a efetividade da AN associada à AG comparada à AG isolada para a cirurgia de revascularização miocárdica relativa à redução da mortalidade.

**Métodos:** Foram analisados mortalidade, arritmias, acidente vascular cerebral (AVC), infarto miocárdico (IM), tempo de internação hospitalar (TIH), tempo de internação em unidade de terapia intensiva (TUTI), reoperações, transfusão sanguínea (TS), qualidade de vida, grau de satisfação e disfunção cognitiva pós-operatória. A diferença média (DM) ponderada foi estimada para as variáveis contínuas e risco relativo (RR) e a diferença de risco (DR) para variáveis categóricas.

**Resultados:** Analisados 17 artigos originais. Metanálise da mortalidade (DR = -0,01; IC 95% = -0,03 a 0,01), AVC (RR = 0,79; IC 95% = 0,32 a 1,95), IM (RR = 0,96; IC 95% = 0,52 a 1,79) e TIH (DM = -1,94; IC 95% = -3,99 a 0,12) não demonstraram significância estatística. Arritmia foi menos frequente com AN (RR = 0,68; IC 95% = 0,50 a 0,93). O TUTI foi menor no com AN (DM = -2,09; IC 95% = -2,92 a -1,26).

**Conclusão:** Não se observaram diferenças estatisticamente significantes quanto a mortalidade. A combinação de AN e AG mostrou menor incidência de arritmias e menor TUTI.

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**Introduction**

Coronary artery bypass grafting occurs in approximately 800,000 patients annually.<sup>1</sup> There is an increased interest in the use of neuraxial anesthesia (NA), spinal and epidural anesthesia, associated with general anesthesia (GA) for coronary artery bypass, which is also a matter for further research worldwide.<sup>2</sup> The risks and benefits of NA in this setting have been reviewed in adult patients.<sup>2</sup>

One of the benefits of NA is to mitigate the response to surgical stress due to blockage of cardioaccelerator fibers, T1 to T5, and improved coronary response to vasodilators improving the balance between the supply and consumption of myocardial oxygen.<sup>2,3</sup> Sympathetic activation is considered the main mechanism for the occurrence of new myocardial infarction in the postoperative period.<sup>3</sup>

The use of NA in heart surgery is still controversial due to the possibility of hematoma or abscess at the puncture site and the possibility of spinal compression.<sup>4</sup> The current data available in the literature were used in mathematical models to estimate the maximum risk of this event after full heparinization, which was estimated at 1:2400 with full heparinization.<sup>4</sup>

The aim of this study was to perform a meta-analysis to evaluate the effectiveness of neuraxial anesthesia associated with general anesthesia compared to general

anesthesia alone for coronary artery bypass grafting regarding the reduction of mortality.

**Method**

Systematic review was performed following a protocol developed prior of the performing this review. This protocol, as well as the review performance, followed the steps suggested by The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>5</sup> The stages of this research were: systematic literature search, careful analysis for inclusion and exclusion of studies, analysis of the quality of studies, data collection of outcome variables, meta-analytic calculations, analysis of sensitivity and homogeneity, and trial sequential analysis. All stages performed are described below.

**Search strategy**

The identification and systematic search for potentially relevant original articles was performed in the following databases: Medline via PubMed from January 1966 to January 2014, Cochrane Central Register of Controlled Trials (CENTRAL) n° 3 (2014), Excerpta Medica Database (EMBASE) from January 1974 to January 2014, and *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (Lilacs) from January 1982 to January 2014. The references of included

studies were also analyzed for articles that had the potential to be part of this review, but they were not identified in the electronic databases. We searched for published studies comparing the use of NA associated with GA and GA alone for coronary artery bypass grafting. The following terms were used in different combinations: Anesthesia, General; *Anesthesias, Intravenous; neuraxial anesthesia, Anesthesia; Epidural, anesthesia, spinal, thoracic surgical procedures*, and *clinical trials as topic*. The search was limited to clinical trials of random allocation that included adult patients (over 18 years old) who underwent surgery only for coronary artery bypass. There was no language restriction.

### Inclusion and exclusion criteria of the studies

Inclusion criteria were clinical trials with random allocation that assessed patients undergoing coronary artery bypass and compared the NA techniques associated with GA and GA alone with or without catheter.

Exclusion criteria were original articles of clinical trials with inadequate description of variables of interest for this review, when the allocation for coronary artery bypass grafting was associated with another type of surgery, when the variables were not of interest to this systematic review, and when an intervention other than NA or GA was used in the patients studied.

Studies initially identified by reading the titles and abstracts that seemed relevant to this review were grouped together for full reading by two reviewers. Disagreements were resolved by consensus meetings. If the disagreements were not resolved, the participation of a third author was planned, but it was not necessary.

### Critical analysis of the studies' quality and classification

The classification of studies was carried out individually and independently by two reviewers, who scored the original articles according to its methodological quality, according to the criteria of Jadad.<sup>6</sup> The evaluated criteria were random assignment of subjects to groups, adequacy of the random allocation, concealment of individuals in groups, adequacy of concealment of individuals and the description of losses and exclusions. A total of 5 points could be achieved with good quality articles being considered those that reach more than 2 points. This criterion was not used to exclude original articles of meta-analytic review.

The Agreement Kappa Index was used to assess whether there has been agreement among the reviewers or if their analysis were consistent among themselves. This statistical test was used considering a statistical power of 80% and type I error probability of 5%. The values of this test may vary between 0 and 1 with 0 being the absence of agreement and 1 perfect agreement between reviewers. Values above 0.8 were considered as good agreement between reviewers.

### Outcome variables and data extraction method

The primary outcome variable was mortality. The variable mortality was considered for the first 7 days of

hospitalization (immediate), between 7 and 30 days after surgery (early), and after 1 year of follow-up (late). Secondary outcome variables were arrhythmias, stroke, acute myocardial infarction, length of hospital stay measured in days, length of intensive care unit stay measured in days, reoperation frequency, blood transfusion measured by the number of participants who received blood transfusion, quality of life, degree of satisfaction, and postoperative cognitive dysfunction.

Two reviewers independently collected the data. One of the reviewers entered the data into a computer program and later, in a second stage, the other reviewer who collected the data checked to prevent the insertion of exchanged numbers into the computer program. The meta-analytic calculations were performed only after the checking by the second reviewer.

### Meta-analysis

The Review Manager software was used to perform the meta-analysis calculations.<sup>7</sup> It was planned to calculate the magnitude of the interventions' effect and the respective 95% confidence intervals (95% CI) for dichotomous variables using relative risk (RR), however, if the event frequency was absent in an analyzed variable included in the original article, the risk difference (RD) was used. The interval variables were evaluated by mean differences (MD). The random-effects model was applied for meta-analytic calculations. Statistical heterogeneity was quantified using the  $I^2$  test. When the values of  $I^2$  were greater than 30%, the results were considered heterogeneous.

Publication bias was investigated by the analysis of inverted funnel plot.<sup>8</sup> The original article from the published study that has been identified as a source of publication bias for the results was excluded during the analysis of sensitivity and homogeneity. The original articles used in the calculations were indicated by the last name of the first author followed by the year of publication to present the meta-analysis results.

### Analysis of sensitivity and uniformity

The sensitivity analysis was performed by comparing separately the results of studies of good and poor methodological quality.<sup>8</sup> The search for statistical heterogeneity was performed by successive meta-analysis, withdrawing a study at a time until the identification of the heterogeneity source. The heterogeneity search was performed in meta-analysis with  $I^2$  test greater than 30%.

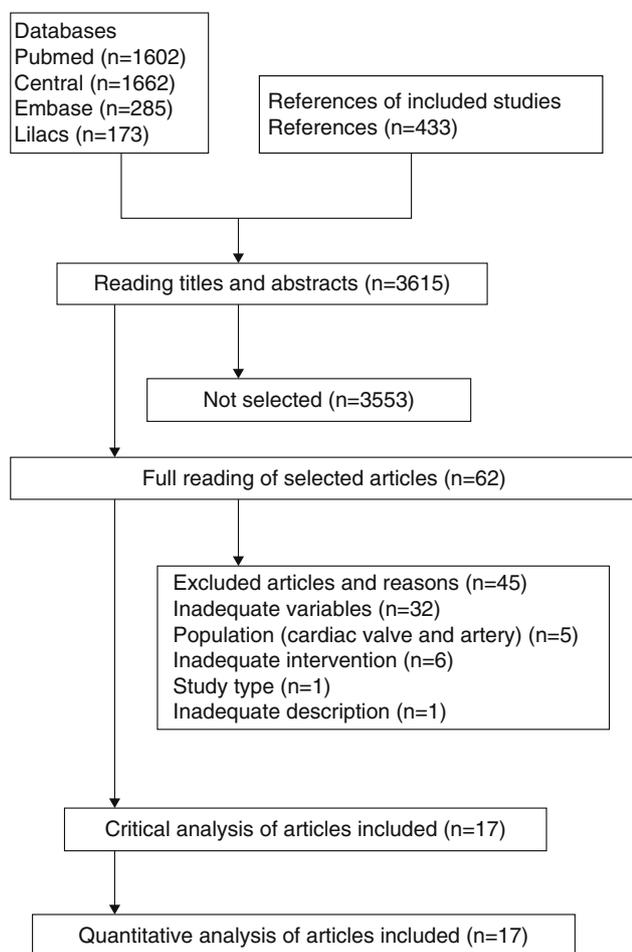
### Trial sequential analysis

We plan to use the trial sequential analysis (TSA) for the variable mortality.<sup>9</sup> TSA provides limits that are intended to monitor the values for the magnitude of the effect being evaluated in an intervention, so that subsequent meta-analysis can generate reliable results.<sup>9</sup> A part of the TSA calculation provides an estimate of how many extra participants need to be assessed in the meta-analysis for the results to be reliable.<sup>9</sup>

The estimate calculation of how many patients would be needed to obtain viable conclusions was obtained by multiplying the sample size calculation result for individual searches performed in a conventional manner by an adjustment factor based on the existing diversity (heterogeneity) between the studies.<sup>9</sup> Conventional calculation to estimate the sample size was performed by considering conventional values (type I error probability of 5% and statistical power of 80%). These calculations were performed using the late mortality incidence value, seen in the GA group, found in this systematic review and aiming at a relative risk reduction of 25%. The adjustment factor based on diversity used was 50%, considering that the statistical heterogeneity above this value is considered high.

## Results

We identified 3615 titles and abstracts by the search strategy and also by analyzing the references of studies that were selected for the assessment of methodological quality. We identified 17 original articles that met the inclusion criteria of this systematic review (Fig. 1).<sup>10–26</sup> The total number of patients studied in the 17 articles identified was 2477. The Kappa Index Agreement between reviewers was 0.92.



**Figure 1** Flowchart of the included and excluded studies according to PRISMA statement recommendation.

Table 1 shows a summary of the studies included in the meta-analysis.<sup>10–26</sup>

## Primary outcome

The primary outcome was assessed in 11 original articles with different follow-up times.<sup>10–13,16,17,20,21,23,25,26</sup> Therefore, the studies were grouped for analysis according to the follow-up time as immediate (during hospitalization), early (30 days), and late (over 364 days). There was no statistically significant difference in the assessed follow-up times (Fig. 2).

The forest plot shows the risk difference and the corresponding 95% CI for each study (Fig. 2). It is observed that all 95% CI crossed the line of statistical invalidity. The diamond plot in the various follow-up time assessed also crossed the line of statistical invalidity. Considering the immediate mortality a  $p$ -value = 0.74 (RD = 0.00; 95% IC = -0.01 to 0.01; 1274 participants). Considering the early mortality a  $p$ -value = 0.56 (RD = 0.00; 95% IC = -0.01 to 0.01; 714 participants). Considering the late mortality a  $p$ -value = 0.24 (RD = -0.01; 95% IC = -0.03 to 0.01; 730 participants). It is concluded that there was no statistically significant difference regarding the studied parameter. It is observed that there was no statistical heterogeneity in the assessment of immediate mortality ( $I^2 = 0\%$ ;  $p = 0.96$ ), early mortality ( $I^2 = 0\%$ ;  $p = 0.92$ ), and late mortality ( $I^2 = 0\%$ ;  $p = 0.66$ ).

## Secondary outcomes

The secondary outcome arrhythmia was assessed in 11 original articles.<sup>10,19,21,24–26</sup> The analysis in the original articles was performed only during the hospital stay. There was a significant difference in the parameter analyzed (Fig. 3).

The forest plot shows the relative risk and the corresponding 95% CI for each study (Fig. 3). It is noted that the 95% CI of 3 studies did not cross the line of statistical invalidity indicating that NA has a protective effect for the emergence of arrhythmias.<sup>10,12,21</sup> The diamond plot also did not cross the line of statistical invalidity showing a protective effect in favor of NA. This analysis  $p$ -value was equal to 0.02 (RR = 0.68; 95% CI = 0.50–0.93; 1363 participants). It is concluded that there was no statistically significant difference in regarding the studied parameter. It is noted that there was statistical heterogeneity in this variable assessment ( $I^2 = 35\%$ ;  $p = 0.12$ ).

The secondary outcome stroke was assessed in three original articles.<sup>12,21,23</sup> The analysis in the original articles was performed only during the hospital stay. There was no statistically significant difference in the assessed parameter (Fig. 4).

The forest plot shows the relative risk and the corresponding 95% CI for each study (Fig. 4). It is noted that all 95% CI of the 3 original articles crossed the line of statistical invalidity indicating no beneficial effect in the NA and GA combination. The diamond plot also crossed the line of statistical invalidity showing no protective effect in favor of NA. The  $p$ -value for this analysis was equal to 0.62 (RR = 0.79; 95% CI = 0.32–1.95; 1288 participants). It was concluded that there was no statistically significant difference regarding

**Table 1** Summary of studies included in meta-analysis.

Authors	Publication year	Quality score	General/neuraxial (n)	Drugs
Bakhtiary et al. <sup>10</sup>	2007	2	66/66	0.16% ropivacaine, sufentanil 1 µg mL <sup>-1</sup> , CI
Berendes et al. <sup>11</sup>	2003	3	37/36	0.5% bupivacaine, sufentanil 15 a 25 µg, CI
Caputo et al. <sup>12</sup>	2001	3	117/119	0.75% bupivacaine 0.5% bupivacaine, CI
Fillinger et al. <sup>13</sup>	2002	2	30/30	0.125% bupivacaine and 0.0003% clonidine 0.5% bupivacaine, morphine 20 µg kg <sup>-1</sup> , CI
Gurses et al. <sup>14</sup>	2013	2	32/32	0.125% and morphine Levobupivacaine 0.075 mg kg <sup>-1</sup> , fentanyl 2 µg kg <sup>-1</sup> CI
Jideus et al. <sup>15</sup>	2001	1	96/45	0.5% bupivacaine, CI 0.2% bupivacaine and sufentanil NR
Kurtoglu et al. <sup>16</sup>	2009	2	42/34	Morphine dose of 8 µg kg <sup>-1</sup>
Mehta et al. <sup>17</sup>	2004	4	47/53	0.25% bupivacaine, CI
Onan et al. <sup>18</sup>	2013	1	20/20	1% ropivacaine, fentanyl 100 µg, CI 1% ropivacaine with fentanyl
Priestley et al. <sup>19</sup>	2002	3	50/50	0.5% bupivacaine, CI 0.125% bupivacaine and 0.0003% clonidine
Rajakaruna et al. <sup>20</sup>	2013	2	117/109	0.5% bupivacaine, CI 0.125% bupivacaine and 0.0003% clonidine
Scott et al. <sup>21</sup>	2001	3	202/206	0.5% bupivacaine, CI 0.125% bupivacaine and 0.0006% clonidine
Shroff et al. <sup>22</sup>	1997	3	9/12	Morphine 10 µg kg <sup>-1</sup> , fentanyl 25 µg, CI
Svircevic et al. <sup>23</sup>	2011	2	329/325	0.125% bupivacaine and morphine, CI 0.125% bupivacaine and morphine
Tenenbein et al. <sup>24</sup>	2008	2	25/25	0.75% ropivacaine, hydromorphone 200 µg, CI 0.2% ropivacaine and hydromorphone
Turker et al. <sup>25</sup>	2005	5	23/23	Morphine 0.01 mg kg <sup>-1</sup>
Vries et al. <sup>26</sup>	2002	2	30/30	0.25% bupivacaine, sufentanil 25 µg 10 mL <sup>-1</sup> , CI

n, number of participants; CI, continuous infusion; NR, not reported.

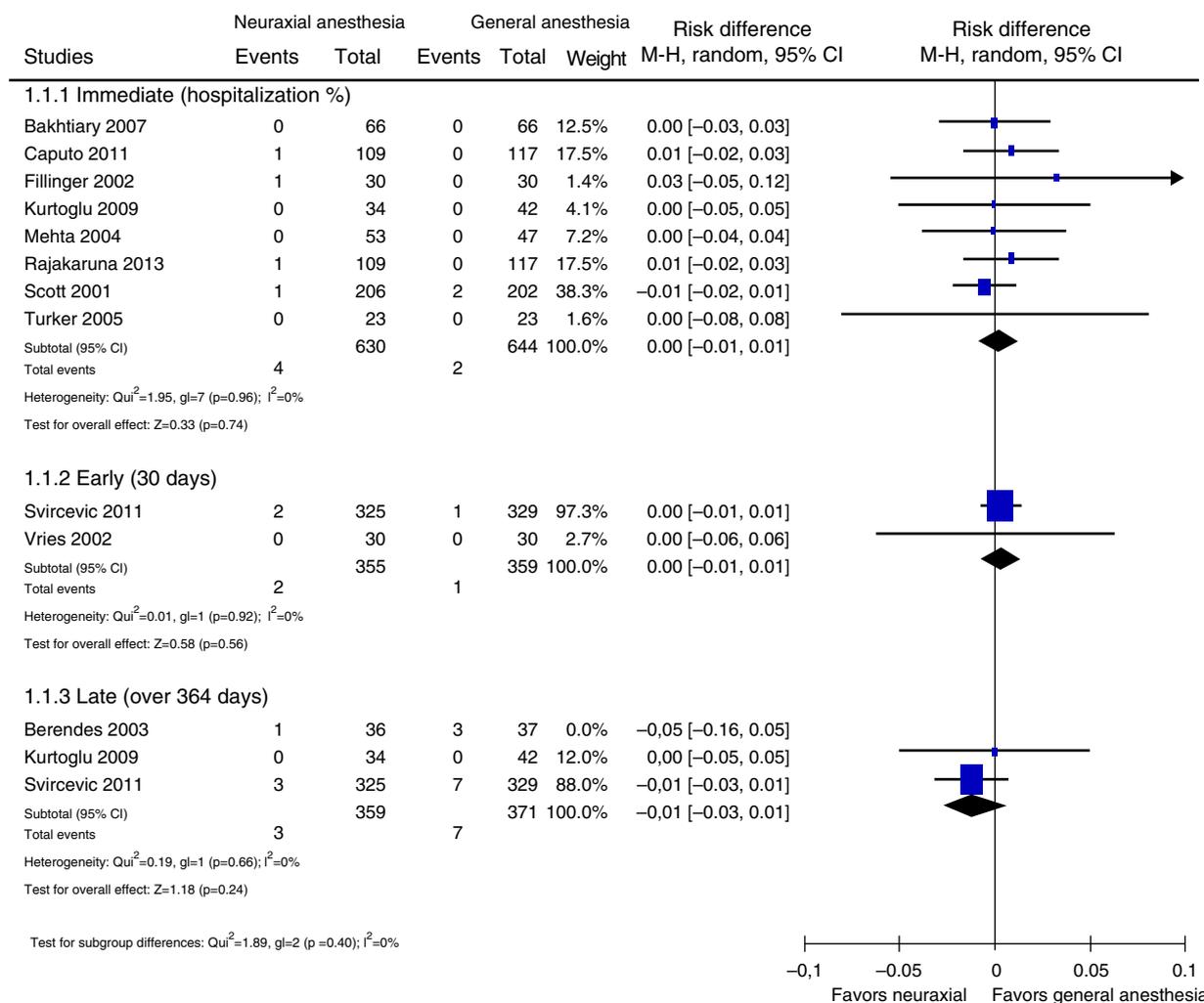
the assessed parameter. It is noted that there was no statistical heterogeneity in this variable assessment ( $I^2 = 0\%$ ;  $p = 0.41$ ).

The secondary outcome acute myocardial infarction was assessed in three original articles.<sup>12,23,26</sup> The analysis in the original articles was performed only during the hospital stay. There was no statistically significant difference in the assessed parameter (Fig. 5).

The forest plot shows the relative risk and the corresponding 95% CI for each study (Fig. 5). It is noted that all 95% CI of the three original articles crossed the line of statistical invalidity indicating no beneficial effect in the NA and

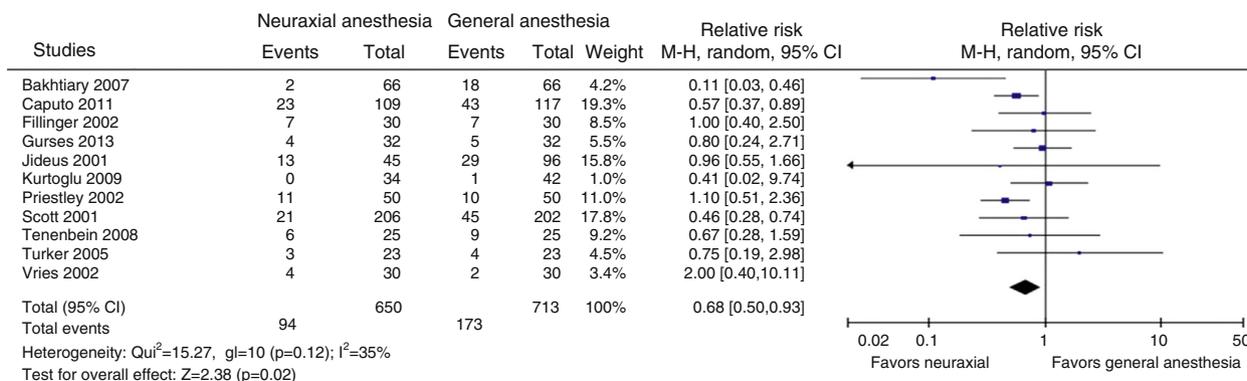
GA combination. The diamond plot also crossed the line of statistical invalidity showing no protective effect in favor of NA. The  $p$ -value of this analysis was equal to 0.90 (RR = 0.96; 95% CI = 0.52–1.79; 940 participants). It is concluded that there was no statistically significant difference regarding the studied parameter. It is noted that there was no statistical heterogeneity in this variable assessment ( $I^2 = 0\%$ ;  $p = 0.61$ ).

The secondary outcome hospital stay was assessed in three original articles.<sup>14,18,26</sup> The analysis in the original articles was performed only during the hospital stay. There was no statistically significant difference in the assessed parameter (Fig. 6).



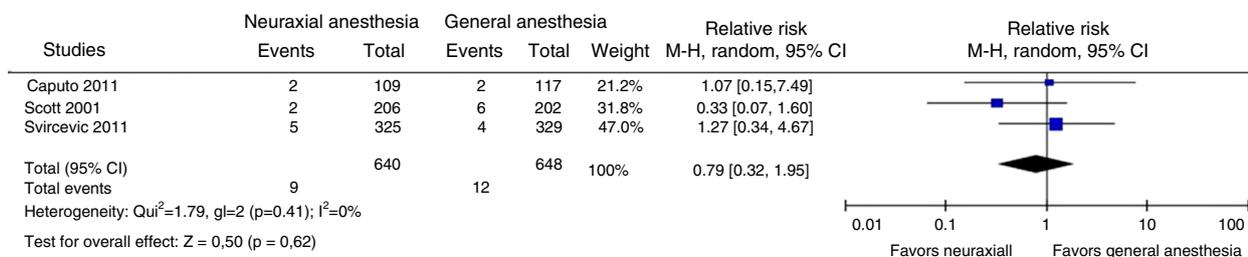
M-H, Mantel-Haenszel; Random, random effect model; 95% CI, 95% confidence interval.

**Figure 2** Evaluation of mortality. M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.



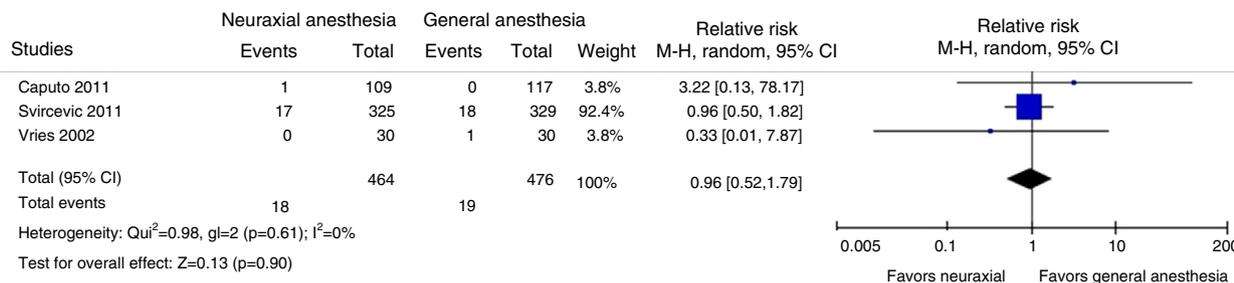
M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

**Figure 3** Evaluation of arrhythmia. M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.



M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

Figure 4 Evaluation of stroke. M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.



M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

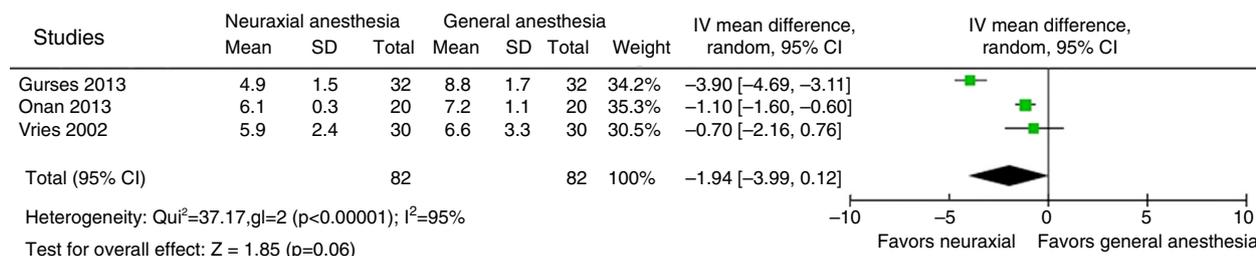
Figure 5 Evaluation of acute myocardial infarction. M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

The forest plot shows the mean difference and the corresponding 95% CI for each study (Fig. 6). It is noted that two 95% CI of the three original articles crossed the line of statistical invalidity indicating that there was a beneficial effect in the NA and GA combination.<sup>14,18</sup> The diamond chart did not cross the line of statistical invalidity showing no protective effect in favor of NA. The *p*-value of this analysis was equal to 0.06 (MD = -1.94; 95% CI = -3.99 to 0.12; 164 participants). It was concluded that there was no statistically significant difference regarding the assessed parameter. It is noted that there was statistical heterogeneity in this variable assessments ( $I^2 = 95\%$ ;  $p < 0.00001$ ).

The secondary outcome length of intensive care unit stay was assessed in two original articles.<sup>13,14</sup> The analysis in the original articles was performed only during the hospital

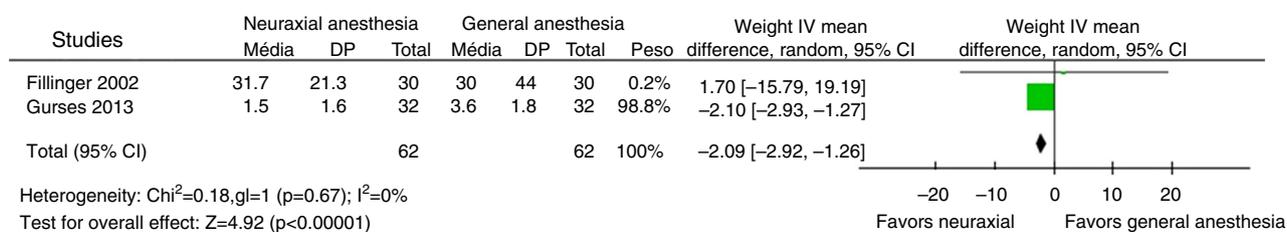
stay. There was a statistically significant difference in the assessed parameter (Fig. 7).

The forest plot shows the mean difference and the corresponding 95% CI for each study (Fig. 7). It is observed that one 95% CI from the two original articles crossed the line of statistical invalidity indicating that there was a beneficial effect in the NA and GA combination.<sup>14</sup> The diamond plot crossed the line of statistical invalidity indicating that there was a protective effect in favor of neuraxial anesthesia. The *p*-value of this analysis was less than 0.00001 (MD = -2.09; 95% CI = -2.92 to -1.26; 124 participants). It was concluded that there was no statistically significant difference regarding the studied parameter. It is noted that there was no statistical heterogeneity in this variable assessment ( $I^2 = 0\%$ ;  $p = 0.67$ ).



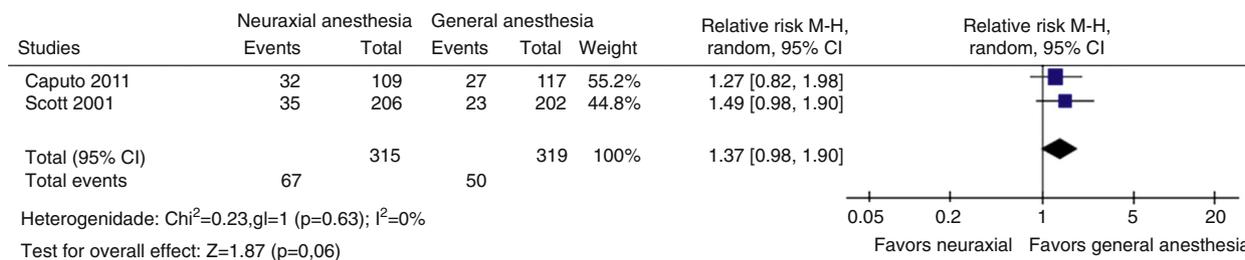
IV, interval variable; random, random effect model; 95% CI, 95% confidence interval.

Figure 6 Evaluation of hospital stay. IV, interval variable; random, random effect model; 95% CI, 95% confidence interval.



IV, interval variable; random, random effect model; 95% CI, 95% confidence interval.

**Figure 7** Evaluation of length of intensive care unit stay. IV, interval variable; random, random effect model; 95% CI, 95% confidence interval.



M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

**Figure 8** Evaluation of blood transfusion. M-H, Mantel-Haenszel; random, random effect model; 95% CI, 95% confidence interval.

The secondary outcome blood transfusion was assessed in two original articles.<sup>12,21</sup> The analysis in the original articles was performed only during the hospital stay. There was no statistically significant difference in the assessed parameter (Fig. 8).

The forest plot shows the relative risk and the corresponding 95% CI for each study (Fig. 8). It is noted that the two 95% CI of the original articles did not cross the line of statistical invalidity indicating that there was no beneficial effect in the NA and GA combination. The diamond plot has not cross the line of statistical invalidity indicating no protective effect in favor of NA. The  $p$ -value of this analysis was equal to 0.06 (RR=1.37; 95% CI=0.98–1.90; 634 participants). It is concluded that there was no statistically significant difference regarding the studied parameter. It is noted that there was no statistical heterogeneity in this variable assessment ( $I^2=0\%$ ;  $p=0.63$ ).

The secondary outcome quality of life was analyzed in one study.<sup>12</sup> The meta-analytic calculations could not be performed. Individual data from this study show that the best result was found in the NA group combined with GA.

The secondary outcomes reoperation frequency, degree of satisfaction, and postoperative cognitive dysfunction were not assessed in any study selected for quantitative analysis of the results.

### Sensitivity and uniformity analysis

The sensitivity analysis was performed for the primary outcome and for the following secondary outcome variables: arrhythmia, stroke, acute myocardial infarction. The

variables length of hospital stay, length of stay in intensive care unit, and blood transfusion could not be analyzed because the studies were classified in the same category.

There was no statistically significant difference between studies of good and bad quality regarding the variable mortality. Considering the group of good quality studies,  $p$ -value=0.55 (RD=0.01; 95% CI=-0.01 to 0.03; 372 participants). Considering the group of bad quality studies,  $p$ -value=0.40 (RD=0.00; 95% CI=-0.01 to 0.01; 1208 participants).

The arrhythmia variable showed that the studies of good quality are statistically significant, those of poor quality have no statistically significant difference, and the analysis of all the articles does not change the end result, confirming that NA associated with GA reduces the incidence of arrhythmias. Considering the group of good quality studies,  $p$ -value=0.004 (RR=0.60; 95% CI=0.43–0.85; 780 participants). Considering the group of bad quality studies,  $p$ -value=0.63 (RR=0.91; 95% CI=0.62–1.33; 451 participants). Considering all the good and poor quality studies,  $p$ -value=0.002 (RR=0.69; 95% CI=0.55–0.87; 1231 participants).

The stroke variable showed no statistically significant difference between the studies of good and bad quality. Considering the group of good quality studies,  $p$ -value=0.31 (RR=0.53; 95% CI=0.15–1.80; 634 participants). Considering the group of bad quality studies,  $p$ -value=0.72 (RR=1.27; 95% CI=0.34–4.67; 654 participants).

The acute myocardial infarction variable showed no significant difference between the studies of good and bad quality. Considering the group of good quality studies,  $p$ -value=0.47 (RR=3.25; 95% IC=0.13–80.60;

226 participants). Considering the group of bad quality studies,  $p$ -value = 0.76 (RR = 0.90; 95% CI = 0.47–1.75; 714 participants).

Statistical heterogeneity occurred in the arrhythmia and hospital stay analyzes. In the arrhythmia variable analysis, the successive meta-analysis method allowed the identification of a study as the source of heterogeneity.<sup>10</sup> The inverted funnel plot showed that this study is responsible for publication bias and its exclusion makes the analysis homogeneous without changing the beneficial effect of using the NA and GA combination. The meta-analysis result without the study responsible for the publication bias shows that, from this analysis,  $p$ -value = 0.002 (RR = 0.69; 95% CI = 0.55–0.87; 1231 participants;  $I^2$  = 0%;  $p$  = 0.46). The original article responsible for the source of statistical heterogeneity of the length of hospital stay variable analysis was identified.<sup>14</sup> The statistical heterogeneity may have a medical explanation, as a catheter was used in cervical space with caudal-to-thoracic segments introduction, unlike other studies performing thoracic catheter insertion. The analysis without the study identified as the source of statistical heterogeneity shows significant results,  $p$ -value < 0.0001 (MD = -1.06; 95% CI -1.53 to -0.59; 100 participants), and favorable to the use of NA.

### Trial sequential analysis

The TSA could not be performed due to the limitation of data found in the articles included in this systematic review for the mortality variable. The low frequency of the event and the limited number of participants limited the calculation.

The number of studied patients required for the meta-analysis results to be considered reliable was estimated. The event rate in the control group (GA group) of this systematic review was 2% (7/371). The 25% relative risk reduction reduced this value to 1.5%. The sample size calculation with a type I error probability of 5% and statistical power of 80% indicated the need for 4664 participants. The sample size was multiplied by the adjustment factor based on the diversity among studies, leading to an estimated 9264 more participants to make our conclusion reliable for the mortality variable.

### Discussion

Briefly, the results of this meta-analysis are: (a) lack of statistical significance between the two anesthetic techniques used for coronary artery bypass, regarding mortality; (b) lower incidence of arrhythmias when NA was used; (c) shorter length of stay in the intensive care unit when NA was used.

There are some limitations in this systematic review. First, we note the existence of heterogeneity among studies in some analyzes; however, the strategy used for the analysis of sensitivity and homogeneity was effective to identify the source of statistical heterogeneity that was explored by the reviewers. Second, the arrhythmia variable showed statistical difference in favor of NA, but excluding the studies using clonidine in neuraxial blockade and not using it in the group receiving GA alone, that statistical significance does not occur demonstrating that possibly the beneficial

effect of using NA for coronary artery bypass may be related to the  $\alpha$ 2-adrenergic agonist effect of this drug when used via epidural route. Third, the number of studies used in the analysis of the length of stay in intensive care unit variable was small, and the result may have occurred by chance.

Stroke, acute myocardial infarction, hospital stay, and blood transfusion variables were not statistically significant considering the data from the studies included in this systematic review. The analysis of these variables may have been limited by the small number of identified studies, small number of events reported in studies, and identification of studies with small samples. The lack of statistically significant difference may be due to the small statistical power present in these analyzes.

The sensitivity analysis that evaluated the results of good and poor quality studies was not a limitation to this research, as the separation of studies to perform the meta-analysis did not change the final results or the conclusions drawn from the analyzes of the full set of original articles. The homogeneity analysis of the length of hospital stay variable showed that statistical significance occurs when the source of statistical heterogeneity is excluded from the meta-analysis, showing that the result for this variable is unbound.

Quality of life was evaluated in a study.<sup>12</sup> The variable presence in only one study prevents the execution of the meta-analysis calculations.<sup>8</sup> The study in question also could not have been included in the analysis because it assessed only the participants who lived in one of the countries participating in the study, and this could be considered data measurement bias.<sup>8</sup>

Reoperation frequency, degree of satisfaction, and postoperative cognitive dysfunction variables were not evaluated in the included studies, highlighting the need for more randomized trials with adequate statistical power and good methodological quality to evaluate the relevant clinical variables. A clinical trial with random allocation performed individually should consider an adequate statistical power for its execution. Considering the 5% mortality in the group undergoing GA, the 3% mortality in the NA alone group, a statistical power of 80%, and a type I error probability of 5%, it is needed 1500 participants in each analysis group.

The maximum number of participants assessed in this systematic review for the mortality variable was 1274, of which 714 for mortality up to 30 days after surgery and 730 for late mortality. The execution of part of the TSA calculation indicated that it necessary to evaluate 9264 extra participants. Considering the execution of this calculation and the number of study participants, we note that the number of participants was small, which implies the existence of a high probability for the presence of type II error in this systematic review that may have been responsible for the lack of statistical significance in the primary outcome.

A systematic review published in 2009 evaluated the use of spinal anesthesia in heart surgery, but concluded that the use of NA was unfavorable, considering the mortality, myocardial infarction, and hospital stay variables.<sup>27</sup> That review analyzed studies in the setting of heart surgery and not only coronary artery bypass, thus differing from our systematic review.

A systematic review published in 2011 evaluated the use of epidural analgesia in heart surgery.<sup>28</sup> The authors concluded that the use of NA is beneficial, considering the reduced risk of postoperative supraventricular arrhythmias and respiratory complications. That review did not individualize data for coronary artery bypass. The authors used an instrument not validated to assess the methodological quality of the included studies, contrary to this systematic review that used an established system for the analysis of this item.

A systematic review published in 2012 evaluated the use of epidural anesthesia in heart surgery.<sup>29</sup> The only assessed variable was the presence of atrial fibrillation, but the results showed marked heterogeneity whose source was not identified by the authors, contrary to this systematic review.

Our study has emerged as an attempt to optimize the results that were found in other systematic reviews in the literature, individualizing the data for coronary artery bypass and to update the knowledge based on scientific evidence in this area of knowledge in order to assist the physician in making decisions before the patient when choosing the anesthetic technique. From this systematic review, we conclude that the combination of neuraxial anesthesia and general anesthesia for coronary artery bypass showed no statistical difference in mortality and is associated with a lower incidence of postoperative arrhythmias and shorter length of stay in the intensive care unit.

## Conflicts of interest

The authors declare no conflicts of interest.

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