INTRODUCTION

Major surgical procedures increase the risk of fatal events. For this reason, influence of anesthetic techniques employed is discussed. Anesthesia has the potential to induce physiological changes that may influence patients’ morbidity and mortality. Despite this, several studies have shown that there is a tendency of decrease in mortality rates related to anesthesia.

Neuraxial anesthesia (NA) refers to the use of local anesthetics in the vicinity of the spinal cord in order to abolish the perception of painful stimuli. General anesthesia (GA) refers to the use of drugs that lead to loss of consciousness and, consequently, to the abolition of the perception of painful stimuli. Anesthetic techniques have not undergone major changes in recent decades, except for the appearance of new drugs as well as new therapy strategies for pain and control of postoperative nausea and vomiting.

A systematic review attempts to gather all the empirical evidence that fits into prespecified inclusion criteria to answer a specific research question. Due to the lack of articles proving effectiveness and safety of neuraxial anesthesia in general in major gynecologic surgeries, this systematic review of randomized clinical trials aims to determine effectiveness and safety of NA compared to GA for major gynecologic surgeries, assisting anesthesiologists in choosing the technique to be used.

METHODS

The study has not been submitted to the Research Ethics Committee (REC) because it is research with analysis of secondary data that are available in databases of medical literature as well as in libraries of laboratories and scientific journeys and events involving the topic of this research.

Protocol

A protocol has been developed for the present research and is available with the author, in case there is need of analysis. This systematic review is in agreement with the items proposed in The Preferred
Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The journal, the institution where the study was conducted and the researchers have not influenced the results obtained.

Inclusion criteria

Types of participants: Female patients, older than 18 years, who have undergone some major gynecologic surgery.

Type of study: Randomized controlled trials have been used.

Types of intervention: The intervention group was submitted to NA. The control group was submitted to GA.

Exclusion criteria

Duplicate articles, articles with incomplete data and those not obtained in full were excluded.

Identification of studies

Search strategies were developed to identify original articles from randomized clinical trials related to the topic in the databases selected for this research. Electronic bases selected were: Embase (Excerpta Medica dataBASE), available on: <http://aplicacao.periodicos.saude.gov.br/> (1974 a agosto de 2017); Lilacs (Literatura Latino-Americana e do Caribe em Ciências da Saúde), available on: <http://regional.bvsalud.org/php/index.php> (1982 to August 2017); MEDLINE® (Medical Literature Analysis and Retrieval System Online), via free search engine PubMed (1966 to August 2017) and freely accessible web search engine Google Scholar (August 2017 2017).

A search strategy was created for the PubMed database. The strategies of all databases were based on the PubMed search strategy. The search strategy on Embase was: “general anesthesia’/exp OR ‘spinal anesthesia’/exp OR ‘epidural anesthesia’/exp AND rand* AND ‘gynecologic surgical procedures’/exp”. The search strategy used on Lilacs was “general anesthesia OR spinal anesthesia OR epidural anesthesia OR gynecologic surgery OR controlled trial.” The search strategy used on Google Scholar was “general anesthesia’, ‘spinal anesthesia’, ‘epidural anesthesia’, ‘gynecologic surgery’, ‘randomized controlled trial’ OR ‘controlled clinical trial’”. There were no restrictions on language, date and format of the document. The search strategy used in PubMed is as follows:


Selection of studies

Titles, abstracts or both, identified through the search strategy in each electronic database, were independently analyzed by two researchers (CAJAIBA, L. S.; REIS, M. R.). Articles that met the eligibility criteria were obtained in full for reading. Contact through e-mail correspondence was tried with some authors to clarify doubts about the study variables, unsuccessful though.

The authors recorded the data extracted from the randomized controlled studies in standardized forms, including: method used, number of participants, inclusion and exclusion criteria, age, country where the study was developed, description of interventions of control and intervention groups, continuous and dichotomous variables and references of the studies. In addition, a scale of quality registered in each form was applied. Disagreements were resolved through consensus meetings.

METHODOLOGICAL QUALITY

The validation of randomized controlled trials was done independently by two authors (CAJAIBA, L. S.; REIS, M. R.) using the Quality Scale and disagreements resolved at a consensus meeting. Criteria for the quality scale evaluation used in this research were: randomization, double-blind masking and set of losses and exclusions.

For randomization: the random sequence generation method was considered appropriate when it allowed each study participant to have the same chance of receiving each intervention and when the investiga-
tor could not predict what the next treatment would be. For double-blind masking: studies were considered double-blind when the double-blind expression was used. The method was considered appropriate when neither the patient nor the data collector were able to identify the type of treatment given to each one or, in the absence of this statement, whether the use of identical placebos or imitations was mentioned. For losses and exclusions: participants who entered the study but did not complete the observation period or who were not included in the analysis and were described by the authors of the original articles. The number and reasons for losses in each group have to be stated. When there are no losses, this should also be stated in the article. When there was no description of losses, zero was assigned to this item.

Maximum of five points could be obtained through this scale, where: one point for each yes, one additional point for an appropriate method of randomization and one additional point for an appropriate method of masking. When the double-blind term was not mentioned but there was a description of the masking of the patient and the researcher of the variables, there was a score on this item in the quality scale. A study was considered of poor quality when it received two points or less in the quality scale.

Variables

Primary variables were mortality, quality of life and degree of satisfaction. Secondary variables include the need for postoperative analgesia, complications in anesthetic recovery room, length of hospital stay, length of stay in post-anesthesia care unit, length of ICU stay, surgical wound infection, other infection sites and blood transfusion.

Data analysis

Statistical analysis was performed with data from the original articles included and referring to the variables of interest to this systematic review. Statistical analysis was performed using the RevMan 5.1 software. For dichotomous variables, the relative risk (RR) and the 95% confidence interval (95% CI) were calculated using the Random Effect Model (REM), and for continuous variables, mean and standard deviation were used to generate mean difference (MD) and 95% confidence interval using REM.

Statistical heterogeneity was quantified by means of the I^2 test. When the I^2 test values were greater than 50%, results were considered heterogeneous.

Analysis of sensitivity and homogeneity

Sensitivity analysis was performed comparing the studies results with good and poor methodological quality. The heterogeneity research was performed by means of successive meta-analyses, with one study being withdrawn at a time until identification of the heterogeneity source. The research was performed in the meta-analyses that presented I^2 test greater than 50%.

RESULTS

Selection of studies

A flowchart demonstrating the selection process of articles relevant to this systematic review is shown in Figure 1. 2,189 titles were analyzed after applying the research strategy, of which 13 were identified as relevant in the process. Four of these were later excluded. Reasons that led to the exclusion are set out in Figure 1. Nine articles were identified as potential to answer the research question. 224 references from these nine selected papers were also analyzed but no study was added because they did not respond to the research question or had already been included. In total, 2,413 titles and abstracts were screened.

FIGURE 1. FLOWCHART DEMONSTRATING PROCESS OF SELECTION OF STUDIES
QUALITY OF STUDIES

Quality analysis of the randomized controlled trials selected for this systematic review showed that: seven articles received three points by the applied quality scale,10–12,14,16,17, one article received two points13 and another article18 only one point. One study has not had the method of randomization described.17 Six studies have not mentioned double-blind masking.10,12–14,16,17 Three studies justified the impossibility of performing double-blind masking.9,11,15 The quality score and main characteristics of the studies are presented in Table 1.

*TABLE 1. MAIN CHARACTERISTICS OF STUDIES SELECTED*

<table>
<thead>
<tr>
<th>Authors (Year of publication)</th>
<th>Type of anesthesia</th>
<th>N</th>
<th>Type of surgery</th>
<th>Main results</th>
<th>Quality score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purwar et al. (2015)</td>
<td>AN</td>
<td>31</td>
<td>Vaginal surgery: Vaginal prolapise; Urinary incontinence</td>
<td>– There was no statistically significant difference between groups regarding nausea, quality of life, as well as duration of PACU, need for postoperative analgesia and length of hospital stay.</td>
<td>3</td>
<td>Use of analgiesics in the first 24 hours after surgery was lower in the NA group. – NA pharmaceuticals: Hyperbaric bupivacaine and fentanyl.</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up time: February 2012 to May 2013. – NA pharmaceuticals: Hyperbaric bupivacaine and fentanyl.</td>
</tr>
<tr>
<td>Segal et al. (2014)</td>
<td>AN + AG</td>
<td>20</td>
<td>Robotic sacrocolpopexy: Vaginal prolapise</td>
<td>– Need for analgesia in percentage of the NA + GA group was 33% and in the GA group was 53% (P &lt; 0.042). – Average satisfaction level was 9.8 ± 0.5 in the NA + GA group and 8.7 ± 1.5 in the GA group (P &lt; 0.014). – The median in relation to the length of hospital stay was equal in both groups: two days.</td>
<td>3</td>
<td>Use of analgesics in the first 24 hours after surgery was lower in the NA group. – Follow-up time: August 2011 to September 2012. – NA + GA pharmaceuticals: Fentanyl and morphine.</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up time: September 2010 to March 2011. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td>Castro-Alves et al. (2011)</td>
<td>AN</td>
<td>35</td>
<td>Abdominal hysterectomy (Benign diseases)</td>
<td>– The median difference in the overall QoR-40 score in 24 hours between NA e GA groups was 17 (11 to 21.5) (p &lt; 0.001). – Patients in the NA group had better scores on recovery quality (P &lt; 0.005). – There was a linear inverse relationship between opioid intake and operative recovery quality in 24 hours, r² = 0.67 (p &lt; 0.0001, 95% CI of 0.77 to 0.51) and in 48 hours, r² = 0.58 (p &lt; 0.0001, 95% CI of 0.72 to 0.42). – The median for nausea in the first 24 hours was 11 in the GA group and 4 in the NA group (P = 0.03).</td>
<td>3</td>
<td>NA provides better recovery quality than GA. Opioid-sparing effects in NA were associated with better recovery quality. In the absence of contraindications, neuraxial anesthesia seems to be an anesthetic plan for these patients. – Follow-up time: September 2010 to March 2011. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up time: September 2011 to May 2013. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td>Wodlin et al. (2011)</td>
<td>AN</td>
<td>91</td>
<td>Abdominal hysterectomy (Benign diseases)</td>
<td>– Neuraxial anesthesia reduced the need for postoperative opioids. – Episodes of vomiting were reported mostly during the first day in the NA group.</td>
<td>3</td>
<td>NA with intrathecal morphine has advantages over postoperative symptoms and recovery after abdominal hysterectomy. – Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td>Wodlin et al. (2011)</td>
<td>AN</td>
<td>91</td>
<td>Abdominal hysterectomy (Benign diseases)</td>
<td>– Medians related to the length of hospital stay were, in the NA and GA groups, 46 and 50 hours (P = 0.4004), respectively. – NA was associated with lower opioid use and higher prevalence of vomiting.</td>
<td>3</td>
<td>Length of hospital stay was &lt; 50 hours, regardless of the type of anesthesia. NA reduced the need for analgesia when compared to GA. – Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td>Follow-up time: March 2007 to June 2009. – NA pharmaceuticals: Hyperbaric bupivacaine and morphine.</td>
</tr>
<tr>
<td>Massicotte et al. (2009)</td>
<td>AN</td>
<td>20</td>
<td>Abdominal hysterectomy</td>
<td>– Morphine intake in the NA and GA groups at 48 h was 19 ± 16 and 81 ± 31 mg (p &lt; 0.0001), respectively. – Nausea at the 6th hour in the GA group had a median of 1. – Times in PACU in the NA and GA groups were 52 ± 9 and 73 ± 11 minutes (P &lt; 0.0001), respectively. – Hospital stay time was 2.2 ± 0.4 and 3.3 ± 0.7 days (P = 0.01).</td>
<td>2</td>
<td>Intrathecal morphine 0.15 mg with 15µg fentanyl reduced postoperative pain and morphine intake in patients with controlled analgesia without increase of adverse reactions in women submitted to abdominal hysterectomy. – Follow-up time: not described. – NA pharmaceuticals: Hyperbaric bupivacaine, fentanyl and morphine.</td>
</tr>
</tbody>
</table>
### VARIABLES

Analysis of the studies allowed us to perform meta-analyses of the following variables: nausea and vomiting, need for postoperative analgesia, length of hospital stay and time in post-anesthesia care unit. Meta-analysis was not possible for the following variables: mortality, quality of life, degree of satisfaction, length of ICU stay, surgical wound infection, other infection sites and blood transfusion. The reasons are described below.

**Mortality:** One study has mentioned mortality. The authors reported that there were no cases of death and it was not possible to perform statistical analysis of this variable. Only with one study it is not possible to perform a meta-analysis.

**Quality of life:** Two studies presented this variable. Two scales were used. In both studies, the SF-36 questionnaire was applied and in one of them was also used the International Consultation on Incontinence Questionnaire on Vaginal Symptoms (ICIQ-VS). As only one used ICIQ-VS, meta-analysis is not feasible, since at least two studies are necessary to perform it. The number of patients who presented satisfactory quality of life in articles using SF36 was not identified.

**Degree of satisfaction:** Two studies presented this variable. In these, different units of measure were used. In one, a verbal scale of 0 to 10 was used. In another, the scale was classified as Very Satisfactory, Satisfactory, Somewhat Satisfactory and Unsatisfactory in relation to anesthesia and post-procedure analgesia.

**Length of ICU stay:** No studies were found with this variable. However, one study reported that two people needed ICU admission, one in the NA group, representing 1.2%, and another in the GA group, representing 1.3%. And another states that there was no admission to ICUs.

**Blood transfusion:** In only one study, this variable was addressed. How many patients needed blood transfusion was mentioned. In patients submitted to GA, three of them had blood transfusion, which represented 3.8% of these individuals. Of those submitted to NA, no patients needed it. Only with one study it is not possible to perform a meta-analysis.

**Infection of operative wound and infection in other sites:** No studies were found with these variables.

**Nausea and vomiting:** This variable was analyzed in six studies. Meta-analysis was only possible with two. No significant statistical difference was
found among studies (RR = 1.48; 95% CI: 0.49 to 4.48; P = 0.48; two studies; 230 participants). Of the four articles in which it was not possible to perform the meta-analysis\textsuperscript{9, 12, 14, 15}, the first one presented the number of people who needed treatment for nausea, being for the NA group 32 people, representing 71% and for the GA group 30 people (68%).\textsuperscript{15} The second one presented the number of people in the median who evolved with nausea at different times in hours after the procedure (6h, 12h, 18h, 24h, 48h), obtaining a non-zero result only at the first moment (6h) for the GA group, equal to 1.\textsuperscript{15} The third one presented the number of people who evolved with nausea from a four-level verbal scale (without nausea, mild, moderate, severe) at different times.\textsuperscript{9} And the fourth one presented the number of vomiting situations in days (day 0, day 1 and day 2) in the different groups.\textsuperscript{12} It was observed that there was significant statistical heterogeneity ($I^2 = 65%$; $X^2 = 2.86$; $P = 0.09$). It was not possible to identify the source of the heterogeneity since meta-analysis is only possible with at least two articles.

Need for postoperative analgesia: Five studies have analyzed this variable.\textsuperscript{10, 13-15, 17} Meta-analysis was possible with two of them.\textsuperscript{10, 17} There was no statistically significant difference in the analysis (RR = 0.76; 95% CI: 0.11 to 5.12; $P = 0.78$; two studies; 54 participants). Of the three studies that did not participate in the meta-analysis, two presented mean in milligrams of the amount of analgesic drugs\textsuperscript{14, 15} and one presented this data in median\textsuperscript{13}. It was observed that there was significant statistical heterogeneity ($I^2 = 88%$; $X^2 = 8.19$; $P = 0.004$), and, therefore, it was not possible to identify the source of the heterogeneity.

Length of hospital stay: This variable was analyzed in five studies.\textsuperscript{9, 10, 14-16} Meta-analysis was possible with two studies.\textsuperscript{14, 15} There was no statistically significant difference (MD = -0.50; 95% CI: -1.67 to 0.68; $P = 0.41$; two studies; 129 participants). Of the three articles in which it was not possible to perform the meta-analysis, the first one presented the variable in median, being for the NA + GA group equal to 2 and for the GA group equal to 2.\textsuperscript{10} The second one presented the mean in hours, being for the NA group 36.4 ± 36.7 and for the GA group 52.6 ± 53.2.\textsuperscript{9} The third one presented the average in days, being for the NA and GA groups equal to 1. Nevertheless, the standard deviation was not informed.\textsuperscript{15} It was observed that there was significant statistical heterogeneity ($I^2 = 96%$; $X^2 = 26.16$; $P = 0.00001$). It was not possible to identify the source of heterogeneity.

Time in a post-anesthesia care unit: Five studies analyzed this variable.\textsuperscript{9, 13-15, 17} It was possible to perform meta-analysis with four of them.\textsuperscript{9, 14, 15, 17} There was no statistically significant difference (MD = -4.81; 95% CI: -24.02 to 14.39; $P = 0.62$; four studies; 205 participants), as shown in Figure 2. In the study in which it was not possible to perform meta-analysis, the variable was analyzed as median hours and for the NA group it was 3.6 and for the GA group, 4.3.\textsuperscript{13} It was observed that there was statistical heterogeneity ($I^2 = 78%$; $X^2 = 13.55$; $P = 0.004$). The heterogeneity test was performed by withdrawing each study successively. One study was identified as a source of heterogeneity.\textsuperscript{14} Analysis without this study did not result in a statistically significant difference (MD = 5.17; 95% CI: -8.16 to 18.50; $P = 0.45$; three studies; 165 participants).

Included in the figure below:

Massicotte et al.\textsuperscript{14}, 2009
Purwar et al.\textsuperscript{9}, 2015
Sprung et al.\textsuperscript{15}, 2006
Vofsi et al.\textsuperscript{17}, 2014

![FIGURE 2. FOREST PLOT OF VARIABLE TIME IN POST-ANESTHESIA CARE UNIT.](image-url)
DISCUSSION

Although some studies point to NA as a good option for postoperative pain control, the impact of this technique on mortality and surgical morbidity is not yet evident. This systematic review was unable to prove greater effectiveness and safety of neuraxial anesthesia compared to general anesthesia for major gynecologic surgeries, since primary variables were not addressed by most of the studies selected.

Some limitations were identified in this systematic review. There were discrepancies in the units of measure and scales presented for variables quality of life, satisfaction, need for postoperative analgesia, length of hospital stay and nausea and vomiting, which made it difficult to perform the meta-analyses. In some cases, contact with the authors was attempted but no answers were obtained. Statistical heterogeneity was identified in the analyses. Exploration was carried out to find the source of this heterogeneity. However, some variables were analyzed with only two articles and results were kept in the text for readers' appreciation.

Variables nausea and vomiting, need for analgesia, length of hospital stay and time in the post-anesthesia care unit were not statistically significant. The small number of events in the studies and a small number of participants identified with these variables may have been some of the limiting factors for analysis.

RR in nausea and vomiting was 1.48, demonstrating that there was no difference between the groups. A systematic review in 2005 evaluated that the GA group had more episodes of nausea than the NA group. Another study reported the lower incidence of postoperative nausea and vomiting in subjects submitted to NA. The two articles used for meta-analysis presented clinical heterogeneity that justified the absence of statistical significance, such as the number of discrepant samples between them.

RR in need of analgesia was 0.76, demonstrating that there was no difference between the groups. The studies used for meta-analysis showed clinical heterogeneity that may have influenced the analysis, such as different surgical techniques, mean age in one of the studies, drugs used in the anesthetic approach and number of samples. In both articles, the authors found that there was no significant difference between the NA and GA groups.

The mean difference in post-anesthesia care unit was -4.81, demonstrating that there was no significant statistical difference between the groups. The studies used for meta-analysis showed clinical heterogeneity that may have influenced the analysis, such as types of surgical techniques, mean age of patients, drugs used in anesthetize approach and sample size.

The mortality variable did not generate meta-analysis. However, the only primary study showed that no cases of death were recorded during the research. It is not the authors’ consensus to evaluate this variable. A systematic review in 2000 showed that neuraxial anesthesia reduces mortality and other types of severe postoperative complications. Another systematic review conducted in 2016 found that the association of NA with GA, when compared to the use of GA, does not have a significant difference in mortality.

The blood transfusion variable has not generated meta-analysis either. However, the only primary study demonstrated that 3.8% of patients in the GA group required transfusion and 0% in the NA group. It is noted that it is not the authors’ priority to analyze this variable.

The quality of life variable, reported in two studies, was expressed in two different scales and in both studies there was no significant statistical difference between the groups. SF-36 is a multidimensional questionnaire that seeks a generic measure of health status consisting of 36 items inserted in eight domains (functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects and mental health). ICIQ-VS is a module of the ICIQ which consists of a comprehensive assessment of severity and impact of vaginal symptoms and related sexual issues, particularly those attributed to pelvic organ prolapse, in order to characterize the severity of these symptoms to measure their impact and evaluate the treatment.
outcome. As the studies analyzed the same variable, however in a different way and with different questionnaires, it is impossible to carry out a meta-analysis for comparative effect.

The degree of satisfaction variable, reported in two studies, was expressed in different scales for evaluation, and in both there was no significant statistical difference between the groups in relation to satisfaction in pain management. As the studies analyzed the same variable, but in a different way and with different questionnaires, it is impossible to carry out meta-analysis for comparative effect.

It is necessary to carry out more randomized controlled trials of good quality and with greater number of participants so that the influence of anesthetic techniques on the variables proposed in this review can be analyzed and, in this way, to guide conducts in the medical area. Based on assumptions of 5% mortality in the general anesthesia group, 1% mortality in the neuraxial anesthesia group, 80% power and 5% level of significance, 284 participants shall be required in each group for future studies in order to answer this research question.

In light of these results, suggestions for future research can be offered. Analysis of mortality, quality of life, degree of satisfaction, complications in the post-anesthesia care unit, length of ICU stay, surgical and other wound infection and blood transfusion are proposed so that it is possible to evaluate the impact of different anesthetic techniques in gynecologic surgeries.

This systematic review has not presented definitive results. Therefore, previous training and daily practical experience over the years shall allow professionals to choose the most effective and safe technique to be employed.

CONCLUSION

To date, evidence assessed from the studies included is insufficient to ensure that neuraxial anesthesia has greater effectiveness and safety compared to general anesthesia for major gynecologic surgeries.

REFERENCES


