Peer Review File

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General information for reviewers

We have made the modifications you have suggested. For those changes that have not been made, we provide support or clarification of the reasons for not doing so.
The first modification is in the title: modifications are highlighted in yellow.
Three tables have been added to address the request by reviewers B and C that we present a subanalysis of those patients who underwent immediate reconstruction. All these reconstructions used a silicone implant placed behind the pectoralis major muscle. All the quantitative variables are expressed as means with standard deviation. We prefer to present the results in this way rather than as means with standard error of the mean. P values have been added in the results section. Also, 95% confidence interval of the differences are included in all tables. The reference suggested by reviewer A has been added together with four other new references to better support the discussion.

Reviewer A

This is a clearly written article and the conclusions are supported by the data presented.

In the patient population studied and with the inclusion/exclusion criteria used, the results of this double-blind, randomized, placebo-controlled, parallel groups clinical trial are consistent in that a single preoperative administration of dexamethasone is effective in decreasing PONV incidence (using the 3-point ordinal scale), reducing pain intensity (using the 0-10 NPRS), reducing further analgesic and antiemetic treatment needs, and producing a faster reversal of decreased respiratory function parameters in women undergoing radical mastectomy with or without breast reconstruction.

I have various minor comments:

Change MSCs to MSc.

Reply: We have modified our text as advised: MSCs **to** MSc.

Changes in the text: page 1, lines: 4, 5, 9 highlighted in yellow.

Correct: of intraalveolar. gases,

Reply: We have modified our text as advised: of intraalveolar. gases **to** of intraalveolar gases.

Changes in the text: page 17, line: 342 and highlighted in yellow.

October 2017 or October 2018?

Reply: We have modified our text as advised: October 2017 or October 2018 **to** October 2018

Changes in the text: page 3, line: 57 highlighted in yellow.

Exclusion criteria included age >70 years of age. But in https://clinicaltrials.gov/ct2/show/NCT02305173, ages eligible for study were 20 Years to 79 Years. Please reconcile.

Reply: We are going to modify the information in NCT02305173: ages eligible for study were 20 Years to 79 **to** ages eligible for study were 20 Years to 69. It was a mistake, sorry.

"Tobacco was used by 13% and 10% patients in the study and control groups, respectively." But Table 1 shows 10% and 14%, respectively. Please correct.

Reply: We have modified our text as advised: Tobacco was used by 13% and 10% patients in the study and control groups, respectively. But Table 1 shows 10% and 14%, respectively **to** Tobacco was used by 9.7% and 15% patients in the study and control groups, respectively.

Since the percentage values can cause confusion, the authors decided to add the raw numbers and percentages in Table 1 and the new table 4.

Changes in the text: Page 12, line 235. Also, the proportions are corrected in table 1 and the new table 4 and highlighted in yellow.

Change surveillance to monitoring.

Reply: We have modified our text as advised: Change surveillance **to** monitoring

Change in the text: Page 17, line 359 and highlighted in yellow.

"A controlled trial is required to determine the usefulness of preoperative steroids and their effects on PONV, pain, and respiratory function." Do you mean: "A controlled trial in this patient population is required to determine the usefulness of preoperative steroids and their effects on PONV, pain, and respiratory function."?

Reply: We have modified our text as advised: A controlled trial is required to determine the usefulness of preoperative steroids and their effects on PONV, pain, and respiratory function. **To:** A controlled trial in this patient population is required to determine the usefulness of preoperative steroids and their effects on PONV, pain, and respiratory function.
Changes in the text: Page 18, lines 381, 382 and 383 and highlighted in yellow.

Figure 1. Change included criteria to inclusion criteria. Correct Candidares **to** Candidates.
Table 2. Change 17.07 to 17.1 and 12.19 to 12.2. Also double-check all %s in Vomiting and Additional Morphine Doses. Change NRS to NPRS.
Table 3. Change 2.06 to 2.1.
Reply: We have modified our text as advised: Figure 1 included criteria **to** inclusion criteria and Candidares **to** Candidates.
Changes in the text: Figure 1 page 26 and both highlighted in yellow.

Reply: Table 2. Change 17.07 **to** 17.1 and 12.19 **to** 12.2. Also, in additional morphine and ondansetron doses: 4.87 **to** 4.9 and 2.43 **to** 2.4, change NRS **to** NPRS.
Changes in the text: Table 2 pages 28 and 29, all of them highlighted in yellow.
Reply: Table 3. Change 2.06 **to** 2.1
Change in the text: Table 3, page 30 and highlighted in yellow.

In references, include the Bakeer´s study (J Pain Res. 19;12:61-67, 2018) which reports on intravenous dexamethasone on efficacy and duration of analgesia (and PONV) of paravertebral block in patients undergoing modified radical mastectomy.
Reply: This reference in included as number 36.
Change in the text: Page 24, lines 496 to 498 and highlighted in yellow.

Reviewer B

- The authors review impact of single dose steroid on outcomes after mastectomy.

- Why was power determined based on expected differences in PONV instead of the other outcomes being examined? PONV improvement with steroids pre op has been demonstrated many times and this was perhaps the "lowest bar" to clear to get a significant and powered outcome. Perhaps if pain or respiratory outcomes was used and more patient accrued, significant findings could have been revealed.

Repy: The authors considered a difference in proportions in the incidence of postoperative nausea and vomiting that we found in a study published by us in 2010 (ref 16), the difference was 35%. Olanders study reported a 40% reduction in the incidence of postoperative pain (ref 17): We choose a 35% difference. The minimum sample size calculated was 35 individuals per group and we decided to bring it to 40 women for each one. Regarding respiratory function, after studying 50% patients, we found a baseline mean forced vital capacity of 2.3 ± 0.9 liters and 6 hours after surgery 1.4 ± 0.4 liters, taking into account an alpha error of 0.05 and a beta error of 0.20 The minimum to study was 32 women per group. Therefore, the authors consider that our size of 41 patients in the study group and 40 in the control provided us with sufficient results to demonstrate significant differences in all outcome variables.
Change in the text: No change.

- p values should be included within the Results section text for all outcomes examined, not just the statistically significant ones. This will avoid misleading the reader.
Reply: We have modified our text as advised: All *P* values related to general clinical characteristics and surgical procedures and the subanalysis of reconstructed patients are included in the results section.
Changes in the text: Pages 12 and 13, lines 233, 234, 235, 236, 238, 241, 242 246, 247, 248, 253, 254, 255, 259, 261, 264, 266, 267, 268 and 270 and highlighted in yellow.

- How many patients had reconstruction? This should be listed in the Results section.
Reply: We have modified our text as advised. As shown in Table 1, all patients underwent MRM, but 20 patients in each group also underwent immediate breast reconstruction in the same surgical procedure (P=0.91).
Change in the text: Page 12, lines 239 to 240 and highlighted in yellow.

- Did the authors consider a subgroup analysis of outcomes in patients with and without recon?
Reply: We added information in the results section: Almost 50% of the patients underwent immediate breast reconstruction. The general characteristics of these patients are described in Table 4. They were younger and had a lower BMI than those women who underwent MRM alone (P=0.002 and P=0.01 respectively), but there were no differences in their allergies, medical history, smoking habits, and previous neoadjuvant chemotherapy (P=0.60, P=0.85, P=0.51, P=0.5). Because the combined procedure was longer than MRM

alone, the operative time, duration of orotracheal intubation, transoperative bleeding, and time to removal of drains were greater than for the MRM only group (P=0.001, P=0.001, P=0.001, P=0.009).

Table 5 shows the intensity of the pain and PONV. Patients who underwent immediate reconstruction had more intense pain at all postoperative points (P<0.05). The incidence of PONV was higher, but the difference was not significant (P>0.1), although these patients had a greater need for narcotics and antiemetics at 6 h and 12 h postoperatively (P<0.05). The respiratory function tests described in Table 6 indicated significant differences in FEV_1, FVC, and PEF up to 12 h after surgery (P<0.05). At 24 h, there was partial recovery of the restrictive pattern, but in patients undergoing immediate reconstruction, these values did not reach the baseline values.

Changes in the text: Pages 13 and 14, lines 257 to 272 and the new tables 4, 5 and 6.

- Were any local anesthetics or blocks used before surgery began? This may also influence PONV.

Reply. We added information in the material and methods section. Local anesthesia or spinal block was not used in any case.

Change in the text. Page 8, line 154 and highlighted in yellow.

- Recommend revising the Discussion for brevity

Reply: The authors have included comments in the discussion on the results of the analysis of patients who underwent immediate reconstruction in contrast to those who only underwent modified radical mastectomy. Likewise, we have discussed information on recently published bibliography as well as that suggested by reviewer A. Fortunately the results of these new references have found agreement with our results, which further support our conclusions.

Changes in the text: All discussion section, pages 14 to 19, lines 277 to 369, new information inserted highlighted in yellow.

Reviewer C

MAJOR

1. Introduction: The first paragraph needs to be reworked as it doesn't flow into your second

paragraph. Your first paragraph should be about why surgery is happening in breast cancer patients. Some of the arguments you have listed are there, but do not relay a strong message. Please work on the 1st paragraph again.

Reply: We have modified our text as advised: GLOBOCAN estimates predicted 18.1 million new cancer cases and 9.6 million cases of cancer-related deaths in 2018 (1). Among these, breast cancer was estimated to contribute 2.1 new million cases (11.6% of overall) and 627,000 cancer-related deaths (6.6% of overall) (1). In Mexico, breast cancer is the leading malignancy causing morbidity and mortality in women (2). Because breast cancer incidence has increased over time, more patients are being treated at advanced or metastatic disease stages. Unfortunately, only 10% of breast cancer cases are detected at an early stage (3). Thus, more patients will likely undergo extensive, radical procedures with or without immediate breast reconstruction (4).

Postoperative nausea and vomiting (PONV) are common complications after surgery (5, 6)

to The Global Cancer Observatory (GLOBOCAN) predicted 18.1 million new cancer cases and 9.6 million cases of cancer-related death in 2018 (1). Among these, breast cancer was estimated to contribute 2.1 million new cases (11.6% of total) and 627,000 cancer-related deaths (6.6% of total) (1). In Mexico, as in many countries, the incidence of breast cancer has grown and it has become the most frequent malignant tumor in women, displacing carcinoma of the cervix, which occupied the first position for many years (2). Despite the implementation of screening programs, breast cancer is only detected early in 10% of patients (3). Therefore, locally advanced disease is still frequently diagnosed. In any case, limited or radical mastectomy is the cornerstone of breast cancer treatment for early or locally advanced disease (4).

Postoperative nausea and vomiting (PONV) and pain have been described as the “big little problem” (5–7).

New reference: 7. Fisher DM. The “big little problem” of postoperative nausea and vomiting: do we know the answer yet? Anesthesiology 1997;87(6):1271–1273

Change in the text: Page 5, lines 71 to 81. A new reference number 7 was added and highlighted in yellow.

2. Justification: The study justification is lacking more evidence. What studies support that PONV and PF are different in the mastectomy group?

Reply: We have modified our text as advised: Radical mastectomy is an extensive surgical procedure involving a mandatory axillary lymph node dissection, resulting in greater bleeding and prolonged surgical time. Hence, this study aimed to evaluate the efficacy of preoperative single-dose steroid administration in decreasing pain and PONV along with its effects on the respiratory function in women undergoing radical mastectomy under general anesthesia for breast cancer with and without breast reconstruction **to** We recently reported the results of a randomized controlled trial of preoperative dexamethasone administration in patients undergoing breast-conserving mastectomy for early breast cancer (18). In that study, we observed a marked reduction in postoperative nausea and a swift reversal in postoperative restrictive pulmonary conditions.

Modified radical mastectomy (MRM) is an extensive surgical procedure involving a mandatory axillary lymph node dissection, which results in greater bleeding and prolonged operative time. This procedure is employed to treat locally advanced breast cancer. There is no evidence on the effect of administration of a single preoperative dose of steroids on respiratory function after this procedure.

Change in the text: page 6, lines 105 to 113 and highlighted in yellow.

3. Methods: The study is lacking a section of "Definitions". Please define at minimum the following terms: breast cancer surgery and PONV. Please also include a definition for variables such as "surgery time" (change to operative time) and bleeding.

Reply: we added the following information: MRM includes the total resection of the mammary gland plus resection of axillary lymphatic nodes. Pectoral muscles were not removed. If it was advisable, immediate reconstruction was performed using a silicone implant placed behind the major pectoral muscle. The operative time was defined as the interval from the skin incision to skin closure. Endotracheal tube removal time was defined as the interval between intubation and endotracheal tube removal. Bleeding was defined as blood loss during the surgical procedure quantified by aspiration of blood and the weight of wet pads and sponges less the weight of dry ones.

Changes in the text: page 9, lines 171 to 177 and highlighted in yellow.

A numeric pain rating scale (NPRS) was used to record pain intensity, in which 0 reflects no pain and 10 reflects the most severe and intolerable pain (20).

Changes in text: page 10, lines 197 to 199.

4. Methods: Please state whether REB approval was obtained.

Reply: We have modified the text as advised: Foot note, ethical statement: The protocol was approved by the Research Ethics Committee of the Specialties Hospital of the Western National Medical Center (ID 2011-1301-74) and was registered with the ClinicalTrials.gov database (ID NCT02305173). Changes in the text: Page 19, lines 403 to 405 and highlighted in yellow.

5. Methods: Who carried out study treatment allocation? Was this a centralized system or an investigator?

Reply: We have modified the text as advised: Allocation took place in a centralized center located outside the hospital whose personnel were blinded to the protocol and patients. The prepared syringes for dexamethasone and placebo were identical.

Changes in the text: Page 7, lines 125 to 127 and highlighted in yellow.

6. Exclusion criteria: Why were women >70yo excluded? With >40% of breast cancer patients being >70yo, I think this exclusion is unjustified. Additionally, were women with respiratory disease excluded?

Reply to the reviewer: Our inclusion criteria did not allow patients over 70 years of age, who due to age are more susceptible to having chronic, uncontrolled, advanced or several degenerative diseases at the same time. The mean age of the women in the study and control group was around 50 years old. Our population is representative since relatively young women undergo breast mastectomy more frequently, at least in Mexico.

No change in the text.

7. Inclusion criteria are not stated. This should be included in the text and Fig 1.

Reply: We have modified our text as advised. Inclusion criteria: Inclusion criteria: Women between 25 and 70 years of age, with a confirmed diagnosis of breast cancer, stages IIA, IIB, and IIIA, American Society of Anesthesiologists (ASA) scores I and II, with or without a history of neoadjuvant chemotherapy, without any type of treatment, such as steroidal and nonsteroidal anti-inflammatory analgesics for four weeks before surgery, and scheduled for unilateral MRM. The women had to have normal kidney and liver function defined as a preoperative creatinine level of <1.2 mg/dL, total bilirubin <1 mg/dL, and no elevation of liver enzymes.

Changes in the text: In figure 1 and the text Pages 7 and 8, lines 132 to 138 and highlighted in yellow.

8. Terms: The terms used to describe the surgeries are confusing and need to be reviewed by a breast surgeon. First the authors have terms to describe surgeries which do not exist. I am not sure what "conservative mastectomy" means (Introduction). Are you talking about lumpectomy? Additionally, the authors have listed "radical mastectomy" in their Results section. A radical mastectomy includes removal of the pectoral muscle, which currently is limited to women with advanced disease. If this is true, please provide more detail on the neoadjuvant treatment these women would have received. I think the lack of inclusion criteria makes it confusing for the reader to understand what population they included. This is then complicated by the use of incorrect terms to describe procedures. Therefore the whole manuscript needs to be revised for this issue.
Reply: We have modified our text as advised. The authors agree with reviewer C. We modify the terms conservative mastectomy for breast conserving mastectomy. We also informed the reviewers that all patients underwent modified radical mastectomy (abbreviation MRM).
Changes in the text: All modifications are made from the title and throughout the manuscript: conservative mastectomy **to** breast conserving mastectomy in figure 1 and the text Page 6 line 106 and highlighted in yellow. Radical mastectomy **to** modified radical mastectomy (MRM):
Changes in the text: page 1 line 2, page 2 line 36, page 3 lines 44 and 46, page 6 line 109, page 7 lines 116 and 121, page 8 line 136, page 8 line 172, page 12 line 239, page 13 lines 259, 262, 263, page 14 lines 279 and 282, page 19 line 389 and highlighted in yellow.

9. Neoadjuvant treatment: 25% of women had some type of neoadjuvant treatment. Please specify what type they received, including last date of treatment as this could impact your results.
Reply: We have modified our text as advised. Five patients in each group required neoadjuvant therapy (P=0.87) with four cycles of doxorubicin and cyclophosphamide (every 3 weeks) and four cycles of docetaxel (every 21 days). The surgical procedure was carried out 1 month after the end of the last chemotherapy cycle.
Changes in the text: page 12, lines 236 to 239 and highlighted in yellow.

10. Results: A separate analysis for women who underwent immediate breast reconstruction is necessary. These women cannot be combined with those who only had a mastectomy as their surgeries are longer, etc. Also, can you provide details about what type of reconstruction they underwent.

Reply: We have added some new information: Almost 50% of the patients underwent immediate breast reconstruction. The general characteristics of these patients are described in Table 4. They were younger and had a lower BMI than those women who underwent MRM alone (P=0.002 and P=0.01 respectively), but there were no differences in their allergies, medical history, smoking habits, and previous neoadjuvant chemotherapy (P=0.60, P=0.85, P=0.51, P=0.5). Because the combined procedure was longer than MRM alone, the operative time, duration of orotracheal intubation, transoperative bleeding, and time to removal of drains were greater than for the MRM only group (P=0.001, P=0.001, P=0.001, P=0.009).

Table 5 shows the intensity of the pain and PONV. Patients who underwent immediate reconstruction had more intense pain at all postoperative points ($P<0.05$). The incidence of PONV was higher, but the difference was not significant ($P>0.1$), although these patients had a greater need for narcotics and antiemetics at 6 h and 12 h postoperatively ($P<0.05$). The respiratory function tests described in Table 6 indicated significant differences in FEV_1, FVC, and PEF up to 12 h after surgery ($P<0.05$). At 24 h, there was partial recovery of the restrictive pattern, but in patients undergoing immediate reconstruction, these values did not reach the baseline values.

Changes in the text: Pages 13 and 14, lines 257 to 272 and highlighted in yellow.

11. Complications: Please provide (in a supplement) the 30d postop complication results.

Reply to reviewer: Surgical morbidity included one seroma observed in the control group, which was drained by puncture without complications.

Page: 14, lines 273 to 274.

12. PRO: Did your team collect any patient-reported outcome (PRO). Is there any data in the literature on this matter, Please address this in the Discussion.

Reply: We added the following information: Patient monitoring was performed directly by the surgeons involved in the surgical procedure. Patients visited them at least twice after surgery. The first visit was for removal of stitches or drainage tube and a second visit 30 days after surgery as end of follow-up. In addition, each patient reported any symptoms directly to surgeons by phone during the 30-day monitoring period.

Changes in the text: Page 11 lines 210 to 214 and highlighted in yellow.

13. Discussion: Please expand on the effect reconstruction has on PONV. This should include a discussion of the sub-group analysis for this population (as recommended above). Please compare your data with that of other studies.

Reply: We added information in practically all the discussion and added 4 new references included the article recommended by Reviewer A.

Discussion

Our results showed that the preoperative administration of dexamethasone (8 mg) markedly decreased pain, PONV, and the need for analgesics and antiemetics after MRM for cancer under total IV anesthesia. Both groups showed marked suppression of respiratory function, but this condition was almost reversed after 24 h in the treatment group. No pulmonary complications were observed in either group. Those patients who underwent reconstruction after the MRM reported more pain and required more analgesics and antiemetics. Although the severity of PONV did not differ significantly different between these patients and those who did not undergo reconstruction, the incidence was higher. This lack of significance was most likely because 50% of the subgroup of reconstructed patients received dexamethasone. Respiratory function in these patients revealed a deeper restrictive pattern that, unlike that in the unreconstructed group, failed to reach baseline values by 24 h after the intervention.

Logistic regression models have identified several risk factors for PONV, enabling adequate prophylaxis in selected patients (21–23). At least four critical risk factors have been identified, including female gender, a history of vestibular diseases and/or previous PONV after surgery, the absence of a smoking history, and opioid use. The incidence rates of PONV were reported to be 10%, 23%, 39%, 61%, and 79% in patients with none, one, two, three, or four of these factors, respectively (24,25).

In addition to these previously described risk factors, the duration of the surgical procedure influences the incidence and intensity of postoperative symptoms; with every additional 30 min of operating time, the presence of pain and nausea increases significantly by up to 60% (23). Although smoking can have a deleterious effect on respiratory function, it appears to offer protection against nausea and vomiting (12). Less than 10% of our

patients smoked and the distribution was comparable in both groups. All patients received opioids during anesthesia, a widely recognized factor in promoting the development of PONV, and those in the control group received more narcotics for pain management.

Since dexamethasone was introduced as an effective antiemetic drug (13), research has established its efficacy in preventing nausea and vomiting after different surgical procedures. The biological actions of glucocorticoids start within 1–2 h of administration; however, the mechanism underlying the antiemetic effect of dexamethasone remains unclear. Reportedly, one possible mechanism could be the central inhibition of prostaglandin synthesis, which hinders the release of endogenous opioids and alters the permeability of the blood–brain barrier to serum proteins (26,27). Glucocorticoids exert analgesic effects primarily through the peripheral inhibition of phospholipase, which decreases the production of metabolites of the cyclooxygenase pathway and the activity of lipoxygenase during the inflammatory response. In addition, the immune response of patients receiving dexamethasone shifts in an anti-inflammatory direction demonstrated by a shift toward suppressed interleukin (IL)-6 and increased IL-10 levels. Patients experiencing less pain suffer fewer postoperative complications (14,15,28).

Several factors, including general anesthesia, can affect pulmonary function via different effects on the respiratory system, e.g., by altering the control of breathing, respiratory muscle activity, residual functional capacity, and distribution of alveolar ventilation/perfusion, or by causing atelectasis. Furthermore, anesthetic agents can affect different areas of the central nervous system that control breathing patterns and respiratory muscle activities (29,30).

An intraoperative reduction in the functional residual capacity of the lungs in the absence of pulmonary comorbidities has been reported; such deterioration occurs at the induction of anesthesia and remains stable intraoperatively (12). Different mechanisms can exacerbate this during anesthesia and after surgery, such as the decreased diameter of the chest wall, changes in the diaphragmatic shape and position, and redistribution of the thoracic blood volume. A reduction in the thoracic diameter is related to a reduction in the inspiratory muscular tone, which could cause alterations in chest wall recoil properties.

Furthermore, compressive dressings used at the end of breast surgery contribute to decreasing the chest wall movement by decreasing the internal diameter of the rib cage,

which decreases the lung volume. Reportedly, the loss of muscle tone and an increase in the intraabdominal pressure could favor a cephalic shift of the diaphragm, contributing to a further reduction in the functional residual capacity (31,32). Atelectasis occurs in almost all patients following general anesthesia, predominantly in the dependent lung zones; mechanisms that could account for its occurrence include small-airway collapse, lung compression, lung surfactant deficiency, and redistribution of alveolar gas. Small-airway collapse is attributed to the reduction in the closing capacity (12). A supine position during surgery promotes atelectasis because of the presence of a gradient in the transpulmonary pressure associated with the increase in the intraabdominal pressure.

Changes in transpulmonary and intraabdominal pressures could result in lung compression and collapse (33). Although the impairment of lung surfactant production remains debatable, the use of volatile anesthetics and high inspiratory oxygen pressure could alter the permeability of the alveolar barrier and inactivate the surfactant. The redistribution of intraalveolar gases in the presence of a high inspiratory oxygen concentration and an increase in the ventilation–perfusion ratio correlate with absorption atelectasis, which is more severe when accompanied by small-airway collapse (32,33). All these etiological mechanisms of postoperative respiratory dysfunction could have contributed to or caused changes in spirometry values in our patients. These changes reflected a restrictive ventilatory pattern, including a decrease in FVC of ≥25%, reduction in FEV_1 with a nearly normal FEV_1/FVC ratio, and reduction in PEF, which reflects a reduction in the chest wall distensibility and decreased expiratory effort (33).

Opioid-induced respiratory depression after surgery is a well-established risk factor, which can be manifest as oversedation, respiratory arrest, and the need for resuscitation. In a review of 357 patients with respiratory depression, 92 cases involved opioids, 53% of which involved opioid use, mainly morphine, for pain control; almost all cases involved multiple modalities of administration and continuous infusion, and 88% of cases occurred within 24 h of the surgical procedure (34). Other risk factors involved in respiratory depression include the use of CNS depressant drugs such as sedatives (barbiturates and antihistamines) and tricyclic antidepressants. However, in the present study, we observed no respiratory depression, possibly because we used opioids only as rescue medication for moderate-to-severe pain and in low dosages with a slow infusion under strict monitoring.

The scientific evidence highlights the prophylactic effect of steroids on pain intensity, the incidence of PONV, and reversal of a restrictive pattern of respiratory function (35). Furthermore, it has been shown that the administration of 8 mg of dexamethasone in the perioperative period can increase the efficacy and duration of a single-shot multilevel paravertebral block in breast cancer surgery and reduce the intensity of postoperative pain, morphine consumption, and PONV incidence (36). The optimum therapeutic effect of dexamethasone appears to be achieved with a single dose of precisely 8 mg intravenously. A higher dose such as 24 mg does not make a difference in pain intensity and PONV incidence after mastectomy; indeed, Steinthorsdottir et al. demonstrated that it increased the incidence of seromas after mastectomy (37).

Our study has some limitations. First, we adhered to a strict anesthesia protocol that is probably unlike the protocols used in the few controlled clinical trials available on this topic (15–18). For example, all patients had a physical status of ASA class I or II and were aged <70 years. We also used opioids, which are recognized to induce PONV, for anesthesia induction and postoperative pain control. However, the protocol for anesthesia induction and postoperative pain control was the same for patients receiving dexamethasone and the placebo. Second, all patients had reduced respiratory parameters in the immediate postoperative period, which recovered to baseline values by 24 h in patients who received dexamethasone. However, our observations were limited to the first 24 h after surgery. Nevertheless, there were no major postoperative morbidities in either group. Third, almost half (40/81) of the patients in our cohort underwent immediate breast reconstruction with silicone prostheses. Autologous reconstruction procedures, such as pedicled transverse rectus abdominis musculocutaneous flaps, were not considered in our study. Hence, our results cannot be extrapolated to patients undergoing such reconstruction procedures because these procedures involve both the chest and abdomen. A controlled trial in this patient population is required to determine the usefulness of preoperative steroids and their effects on PONV, pain, and respiratory function.

14. Conclusion: The study is lacking a conclusion. Please include one in the revision.

Reply: We added the following information: In conclusion, based on our study results and despite its limitations, we propose that preoperative single-dose steroid administration is effective in decreasing PONV incidence and pain intensity and causes a rapid reversal of the restrictive respiratory condition in patients undergoing MRM with or without breast reconstruction.

Changes in text: Page 19 lines 386 to 389 and highlighted in yellow.

15. English: The authors would highly benefit from an English-speaking colleague to review the manuscript. There are far too many examples of where poor translation has occurred or ideas are not clearly worded in English.

Reply: The manuscript was extensively revised by Oleng English three times, been the last two revision to submit the first and second version of the manuscript to Gland Surgery. Certificates are attached.

Minor

1. Revise conservative breast surgery for "breast conserving surgery", which is the standard writing.

   Reply: We have modified the text as advised: conservative breast surgery is change **to** breast conserving surgery.

   Changes in the text: Page 6, line 106. Figure 1 and highlighted in yellow.

2. Introduction: Can you please provide a reference for this: Radical mastectomy is an extensive surgical procedure involving a mandatory axillary lymph node dissection, resulting in greater bleeding and prolonged surgical time.". What are you comparing this to?

   Reply to reviewer: We have modified the text as advised: As noted in the introduction.

   We recently reported the results of a randomized controlled trial of preoperative dexamethasone administration in patients undergoing breast-conserving mastectomy for early breast cancer (18). In that study, we observed a marked reduction in postoperative nausea and a swift reversal in postoperative restrictive pulmonary conditions.

   Modified radical mastectomy (MRM) is an extensive surgical procedure involving a mandatory axillary lymph node dissection, which results in greater bleeding and prolonged operative time. This procedure is employed to treat locally advanced breast

cancer. There is no evidence on the effect of administration of a single preoperative dose of steroids on respiratory function after this procedure.

Changes in the text: Page 6, lines 105 to 113 and highlighted in yellow.

2. Introduction: Please reference this statement: "Because breast cancer incidence has increased

over time, more patients are being treated at advanced or metastatic disease stages." Also clarify how this is true? Are there no screening mechanisms in place?

Reply: There are early detection programs for breast cancer in Mexico. These have been in place for 10 years but are still insufficient. Although it is increasingly common to treat early breast cancer, local and even metastatic disease is still diagnosed. We have modified the text as advised: In Mexico, as in many countries, the incidence of breast cancer has grown and it has become the most frequent malignant tumor in women, displacing carcinoma of the cervix, which occupied the first position for many years (2). Despite the implementation of screening programs, breast cancer is only detected early in 10% of patients (3). Therefore, locally advanced disease is still frequently diagnosed. In any case, limited or radical mastectomy is the cornerstone of breast cancer treatment for early or locally advanced disease (4).

Changes in the text: Page 5, lines 74 to 79 and highlighted n yellow.

3. Limitations paragraph: The authors state they included <60y but their exclusion criteria says >70. Please clarify this.

Reply to reviewer: The inclusion criteria included women younger than 70 years of age, but all the women included in our study were younger than 60 years, which is within the age limit. To prevent confusion, <70 years is left. Page 18, line 372 and highlighted n yellow.