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Research Article

Possible Role of Clonidine in Postoperative Nausea and Vomiting Prophylaxis in Thyroid Surgery: A Retrospective Study

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Abstract

Objective: Clonidine is a sympatholytic drug used mainly for its antihypertensive effects. However, recent studies suggest that clonidine may also be effective as antiemetic drug. Our main outcome was to evaluate the efficacy of clonidine for preventing postoperative nausea and vomiting (PONV) during elective thyroid surgery.

Methods: We conducted a retrospective evaluation of medical charts of adult females who underwent an elective thyroid surgery and received either Clonidine (Clonidine group) or Ondansetron (Ondansetron group).

Results: Sixty patients were included per group (120 total). The incidence of nausea, and vomiting was greater in the Ondansetron group, however, only the difference in the number of patients that experienced vomiting reached a statistical significance ($p = 0.03$). No difference was found in the number of patients that required antiemetic drugs. No statistical significant differences were observed for intraoperative hemodynamic parameters between both groups. We observed a statistical significant difference only for maximum systolic ($p = 0.004$) and minimum diastolic blood pressure ($p = 0.012$).

Conclusion: Clonidine was found to be more effective than Ondansetron in the prophylaxis of postoperative nausea and vomiting. Thus, Clonidine could have a prophylactic role for PONV in females undergoing thyroid surgery. The hemodynamic consequences of using Clonidine as antiemetic rescue instead of other antiemetic drugs needs to be carefully evaluated in future studies.

Keywords: *Clonidine; Ondansetron; Postoperative Nausea and Vomiting; Thyroid Surgery; Anesthesia*

Introduction

Despite continuous improvements in anesthesia practice that have dramatically changed patient satisfaction after anesthesia and surgery, post-operative nausea and vomiting (PONV) still affects 30% of the surgical population and up to 70 - 80% of high-risk patients [1]. PONV represents one of the major causes of dissatisfaction from anesthesia and is at times identified by patients as more disabling than post-operative pain. Serious medical conditions, such as wound anastomosis, dehiscence and aspiration, can be caused by PONV, though these occurrences are rare. Even though PONV is identified as one of the most common adverse effects following general anesthesia, it is often under-diagnosed and under-treated.

Clonidine, an alfa$_2$-adrenergic agonist, is a well-known antihypertensive agent routinely used in the practice of anesthesia for the versatility of its effects, including its uses as an anti-shivering drug, a sedative and as an adjuvant analgesic [2]. It has been found to suppress the opioid withdrawal symptoms and possess antidiarrheal activity in human [3]. Its anti-emetic activity has been investigated in studies involving pediatric patients undergoing strabismus surgery and breast surgery in adults [4]. Post-operative nausea and vomiting often occurs in patients undergoing thyroid surgery, who often have a high Apfel risk score due to their female gender and post-operative opioid use [5]. Therefore, to investigate the use of Clonidine as a prophylactic agent for PONV, we performed a retrospective chart evaluation of medical records to evaluate the efficacy of clonidine for preventing postoperative nausea and vomiting (PONV) in adult female patients undergoing elective thyroid surgery.

Methods

Study design and patient population

This study was approved by the Local Research Ethics Committee. Data were collected by conducting a retrospective evaluation of the medical records of adult female patients undergoing elective thyroid surgery in the Department of Endocrine Surgery. Written informed consent was obtained from all the participants in the study. To ensure confidentiality, patient identifiers were not collected. No pharmaceutical companies were involved in this study. This study adheres to the applicable EQUATOR guidelines. Medical data are collected for all inpatients admitted to our surgical ward by attending physicians and trained nurses using a uniform medical chart format. Only patients that received either Clonidine or Ondansetron intraoperative were enrolled in this study. Which of these two drugs the patients received intravenously determined the group the patients were assigned to: the group of patients that received Clonidine but not Ondansetron was referred as the "Clonidine group", whereas "Ondansetron group" indicated the group of patients that received Ondansetron but not Clonidine.

Inclusion criteria were: age > 18, body mass index (BMI) < 35, American Society of Anaesthesiologist (ASA) I-II, Apfel risk score ≤ 3, Koivuranta score ≤ 3, non-smokers, not undergoing chemotherapy, and total intravenous anesthesia (TIVA) as the anesthetic technique of choice. Patients were excluded if they presented with any of the following characteristics: age < 18, male, smokers, ASA III-IV, Apfel score = 4, Koivuranta score > 4, BMI ≥ 35, patients undergoing chemotherapy, use of volatile anesthetics during the surgery, patients undergoing other surgeries, patients who received both Ondansetron and Clonidine, or patients who received neither of these two drugs, or patients who received Clonidine postoperatively.

As general practice in the study hospital, the conduction of anesthesia and the postoperative surveillance protocol for patients undergoing thyroid surgery presented the following characteristics. General anesthesia was induced using Propofol 1.5 - 2 $mg.kg^{-1}$ IV and Rocuronium bromide 0.6 $\mu g.kg^{-1}$ IV was administered to facilitate tracheal intubation. Patients were placed in the supine position with a hyperextension of the head. Anesthesia was maintained using TIVA with Propofol (4 - 8 $mg.kg^{-1}.h^{-1}$) and Remifentanil (0.25 - 0.5 $\mu g.kg^{-1}.min^{-1}$). Standard monitoring was used and included continuous electrocardiogram, pulse oximetry, non-invasive blood pressure and end-tidal carbon dioxide monitoring. Heart rate and blood pressure were recorded every 5 minutes. During the surgery, patients received Dexamethasone 8 mg, Morphine 0.1 $mg.kg^{-1}$ and Ketorolac 30mg. In accordance with local standard protocol for PONV prophylaxis and treatment, Ondansetron 4 mg was administered intraoperative in the patients at high risk of PONV (Apfel score ≥ 3 or Koivuranta score ≥ 3) or during the postoperative period in patients who experienced vomiting and/or intense nausea. Even more, Ondansetron was administered following the clinical judgment of the anesthetist in charge. Reasons not to use Ondansetron were: drug hypersensitivity, pregnancy, breastfeeding and long Q-T syndrome. Clonidine (0.01 $\mu g.kg^{-1}$) was administered during the surgical period or postoperatively to treat high blood pressure. In our institution, Clonidine is a first-line therapy for intraoperative hypertension. Reasons not to administer Clonidine were: drug hypersensitivity, bradycardia, sick sinus syndrome, atrioventricular block (II or III degree), pregnancy and breastfeeding.

After the completion of the surgical procedure, patients were transferred in the recovery room. The presence and the severity of pain, nausea, vomiting, and sedation was assessed by nurses in the post-anesthesia care unit (PACU). Visual analogue scale (VAS) was used to assess pain. In case of VAS ≥ 4, patients received Paracetamol (1 gr, IV) or Morphine (to a maximum of 0.2 $mg.kg^{-1}$) as analgesic rescue regimen. Metoclopramide (10 mg, IV) or Ondansetron (4 mg, IV) were administrated as antiemetic rescue drugs. The decision of administered Ondansetron or Metoclopramide was based on the presence of contraindication of the drugs. Even more, in the case that patients had already received Ondansetron intraoperative, the patients received metoclopramide.

Patients were transferred to the ward when Aldrete score was ≥ 8 [6] and modified Post Anesthetic Discharge Scoring System (PADSS) was ≥ 9 [7]. In accordance with local standard protocol for post-surgical patients, trained nurses performed the same assessment in the surgical ward. Nausea and vomiting were evaluated as a categorical parameter (i.e. presence or absence), during the post-surgical period. Patients were discharged 24 hours postoperatively.

Data collection

For each patient the following information was recorded: age, BMI, duration of surgery, duration of anesthesia, Propofol and Remifentanil dosage, Morphine dosage, systolic blood pressure (SP), diastolic blood pressure (DP) and heart rate. Heart rate and blood pressure

were recorded every 5 minutes. For each patient, we calculated the Apfen and Koivuranta scores. We also recorded the incidence of PONV and the eventual use of antiemetic drugs during the 24-hour period following the surgical procedure.

PONV was defined as any episodes of nausea, retching or vomiting occurring during the first 24h after surgery in inpatients. The risk of PONV can be calculated using the Apfel score and the Koivuranta score (Table 1) [8,9]. The main outcome of the study was to analyze the number of patients that experience PONV and the use of antiemetic drugs in the Ondansetron and Clonidine groups within 24 hours of surgery.

The Apfel score		The Koivuranta score	
Risk factors	**Points**	**Risk factors**	**Points**
Female gender	1	Female gender	1
History of PONV or motion sickness	1	History of PONV	1
		Motion sickness	1
Postoperative opioids	1	Duration of surgery more than 60 minutes	1
Non-smoker status	1	Non-smoker status	1
Total:	0-4	Total:	0-5

Table 1: *The Apfel and Koivuranta score. Each score is used to predict the risk of PONV on the base of risk factors. These scores assign one point for each parameter and determine the probability to experience PONV according to the total score by adding up the value of the individual factors. The total score obtained from the patients corresponds to the probability to experience PONV.*

The data were entered into a spreadsheet (Microsoft Excel) and analysed using SPSS (IBM SPSS software version 17.0.1). Data are shown as mean ± standard deviation. Shapiro-Wilk test was performed to verify normality of distributions. Quantitative variables were compared by the Mann-Whitney U test or student t-test where appropriate. Chi-squared test was carried out to analyze categorical variables. P values < 0.05 were considered as statistically significant. Power tests (ex post) were performed to estimate the sample sizes, the power was considered appropriate with 1-ß values > 0.8.

Results

Study participants

A total of 120 medical records were identified from the 1st of January 2014 to the 30th of April 2015 that fulfilled our inclusion criteria. Sixty patients for each group were included in the study. All the patients were female, undergoing total thyroidectomy surgery with an Apfel score of 2-3 and a Koivuranta score of 2 - 3. Demographic characteristics and the total amount of perioperative anesthetic and analgesic drugs used are shown in table 2. We did not find a statistical significant difference in morphine administration between the groups (p = 0.1).

	Clonidine Group (n = 60)	**Ondansetron Group (n = 60)**	***P***
Age	45.3 (12)	44.9 (12.5)	0.41
Apfen 2	17 (28%)	14 (23%)	
Apfen 3	43 (72%)	46 (77%)	
BMI	24.7 (3.9)	25.3 (4.4)	0.21
Duration of surgery (min)	55.5 (14.2)	56 (16.7)	0.44
Duration of anaesthesia (min)	68.1 (15.6)	69.9 (17.9)	0.27
Remifentanil (ml)	23.2 (9.6)	27.1 (9.1)	0.01
Morphine (mg)	6.6 (1.2)	6.9 (1.5)	0.1

Table 2: *Demographic Characteristics, Anesthetic and Analgesic drugs dose.*

Value are expressed as mean and standard deviation (SD); BMI: Body Mass Index.

Main results

The number of patients that presented PONV (nausea and /or vomiting) was significantly higher in the Ondasetron Group (p = 0.01). Similarly, evaluating the incidence of nausea and vomiting separately, the number of patients that experienced nausea (21 vs. 28 patients) and/or vomiting (9 vs. 20 patients) was greater in the Ondansetron group. These differences reached statistical significance only for the incidence of vomiting (p = 0.03, as shown in table 3). However, the number of patients requiring antiemetic drugs was identical between the groups (10 vs. 10 patients). There were no statistical significant difference in heart rate, intraoperative minimum systolic and maximum diastolic pressures between the groups (Figure 1). We found a statistical significant difference for maximum systolic (p = 0.004) and minimum diastolic blood pressure (p = 0.012).

	Clonidine Group (n = 60)	Ondansetron Group (n = 60)	*P*
PONV- free	36 (60%)	21 (35%)	0.01
Nausea	21 (35%)	28 (47%)	0.26
Vomiting	9 (15%)	20 (33%)	0.03
Antiemetic' drugs usage	10 (16%)	10 (16%)	1

Table 3: *Number of patients not suffering from PONV (post-operative nausea and vomiting) and the use of antiemetic drugs during the 24-h period following the surgery.*

Values are expressed as number of patients and the corresponding percentage are shown in brackets.

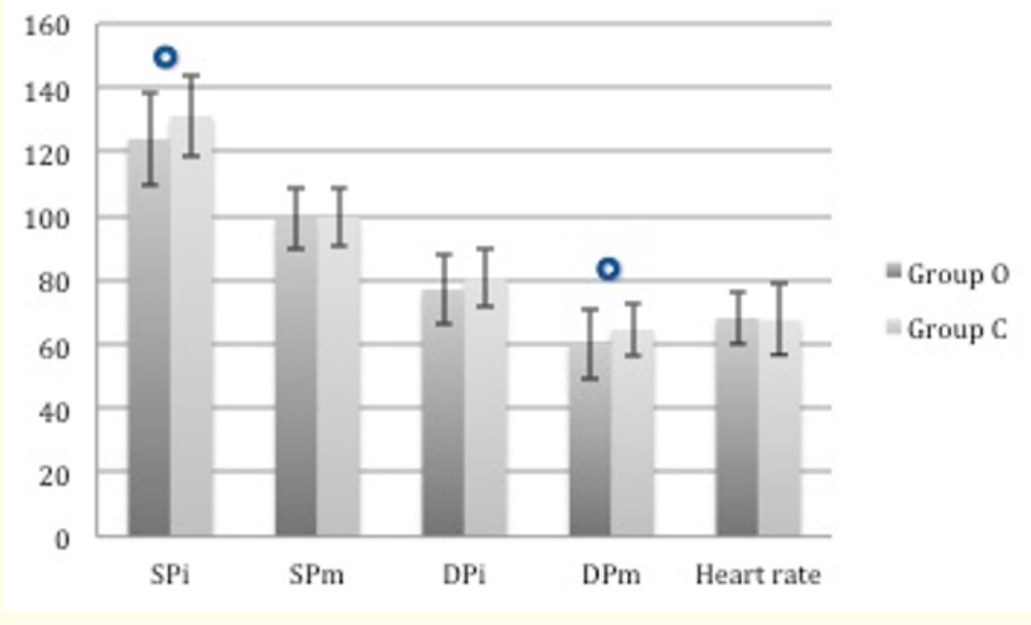

Figure 1: *Intraoperative heart rate, systolic and diastolic blood pressure in the group of patient receiving Clonidine (light grey column) or Ondansetron (dark grey column).*

Data are presented as mean, error bars represent standard deviation. SP: Systolic Pressure; DP: Diastolic Pressure; SPi: Mean Systolic Pressure during Induction of Anesthesia; SPm: Mean Systolic Pressure during Maintenance of General Anesthesia; Dpi: Mean Diastolic Pressure during Induction of Anesthesia; DPm: Mean Diastolic Pressure during Maintenance of General Anesthesia.

°P values < 0.05, statistically significant.

Discussion

In this retrospective evaluation of medical charts, we studied the effects of Clonidine in comparison to Ondansetron on the incidence of PONV and on the use of antiemetic drugs. In the group that received Clonidine, we observed a statistical significant fewer number of patients suffering from vomiting. Antiemetic drugs' usage was identical between the groups. Additionally, Clonidine did not produce a greater hemodynamic alteration during induction and maintenance of anesthesia in comparison to Ondansetron.

Clonidine is an alpha-2 adrenergic agonist with peripheral and central action. Even if it is mainly used as an anti-hypertensive drug, other possible usages are described in the literature: for postoperative pain [10,11], sedation [12], for the treatment of shivering [2], alcohol withdrawal [13] and postoperative nausea and vomiting [14]. The mechanism of its possible anti-emetic effect is still unknown; however, the gastrointestinal effects of Clonidine is documented [15,16]. A 2003 retrospective study [3] evaluated the effect of Clonidine on the opioid withdrawal symptoms in patients undergoing ultra-rapid opioid detoxification (UROD) procedures. The UROD procedure consisted of Naltrexone (300 - 350 mg through nasogastric tube) and/or Naloxone (5 - 15 mg IV) followed by Nalmefene (4 - 12 mg IV) or a combination of Nalmefene (4 mg IV) and Naloxone (25 mg IV) infused for an 8-hour period. Clonidine was administered to all the patients either through a nasogastric tube before the UROD procedure or IV during the procedure. The data were analyzed on the basis of the total dose of Clonidine administered. The authors did not observe a statistically significant difference in the incidence of vomiting and nausea between the groups; however, the incidence of diarrhea was significantly lower in the patients that received high clonidine doses (> 1 mg IV).

A 2001 randomized crossover study [17] evaluated the effect of Clonidine in comparison to placebo on the gastric emptying of solid meal using a wide-filed gamma camera on adult patients with diabetic gastropathy. They did not observe any differences in gastric emptying rates. However, another similar trial [18] reported an accelerated emptying of solid meal after prolonged treatments with Clonidine. Consequently, it is still controversial whether Clonidine plays its gastrointestinal effects in accelerating gastric emptying or reducing gastric sensation [19] or through its central action [20,21].

Nevertheless, the evidence that Clonidine might have an anti-emetic effect is increasing. A randomized clinical trial of 68 patients scheduled for breast cancer surgery [22] evaluated the effects of Clonidine on PONV in comparison to placebo. The patients received IV Clonidine or placebo immediately after intravenous cannulation, before the induction of anesthesia. They observed a significant reduction of PONV and a greater patient satisfaction in the group of patients that received Clonidine. Intraoperative blood pressure was significantly lower in the Clonidine group whereas intraoperative heart rate was similar between the groups. A 2013 pilot randomized crossover trial [23] tested the effectiveness of transdermal Clonidine in comparison to placebo in women suffering from severe refractory hyperemesis. The authors observed fewer incidences of nausea and vomiting and a reduction of antiemetic drug consumption without increasing of the number of adverse effects. Differently from these studies, we carried out a retrospective study and we paid attention to include patients that received either Clonidine or Ondansetron. In this way, we tried to compare the effect of these two drugs on the incidence of PONV. Ondasetron, a serotonin 5-HT_3 receptor antagonist, blocks the serotonin receptors located on neuronal tissues in the peripheral and central nervous systems. This drug is a highly selective and a potent antagonist for this receptor type, blocking the emetic pathway at various points (i.e. the chemoreceptor trigger zone (CTZ) and peripherally in the upper gastrointestinal tract) preventing the emetic reflex. Comparing these two drugs, we obtained similar results of the aforementioned studies. In fact, we observed a reduction in the number of patients suffering from nausea and/or vomiting in the Clonidine group. Our results seem to show that Clonidine is more effective than Ondansetron, for the prophylaxis of PONV.

One possible concern of using Clonidine can be the possible side effects (e.g. hypotension); however, we did not find a significant difference in the hemodynamic parameters of our groups of patients.

Our study presents several limitations. First of all, this is a retrospective study, the available data was extracted from medical charts, consequentially, it was possible to obtain data only on the number of patients that suffer from PONV and the amount of anti-emetic drugs used but not of the number of episodes and the timing after the discharge from the Recovery room. It was not possible to extract other

important data such as the overall patient satisfaction. Secondly, Clonidine was administered intraoperative as an anti-hypertensive drug, therefore, the statistical analysis that we carried out on the hemodynamic parameters might have been influenced from this aspect. In fact, we observed a statistical significant difference in the maximum systolic blood pressure between the groups. This could be explained by the fact that Clonidine was administered for its anti-hypertensive effects, thus it is normal to find a higher systolic blood pressure in the Clonidine group. Thirdly, the study included a small cohort of patients in a specific clinical setting (i.e. thyroid surgery). It is not possible to draw any conclusion as regard the effectiveness of Clonidine in other surgical setting, especially taking into accounts the high variability of the incidence of PONV after different kind of surgeries.

We identified some areas for future research. There is the need of prospective randomized double -blinded study focused on the comparison between Clonidine and other antiemetic drugs used nowadays for the prophylaxis of PONV (i.e. Ondansetron, Dolasetron, Dexamethasone). These studies should consider not only the overall incidence of PONV but also the hospital stay and patient satisfaction. Particular attention should be paid to the analysis of side effects of Clonidine and the risk-benefit implication of using this medication as rescue antiemetic.

Conclusions

In conclusion, our study shows that the use of Clonidine could potentially have a role in the prophylaxis of PONV in female patients scheduled for thyroid surgery. Future prospective randomized double-blinded trials have to be promoted on the effect of Clonidine as an antiemetic drug.

Competing Interest

No external funding and no competing interests declared

IRB Information

This study was approved by the Local Research Ethics Committee of Pisa (protocol number 222, date of approval 25/06/2015).

Bibliography

1. Tramer MR. "A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues". *Acta Anaesthesiologica Scandinavica* 45.1 (2001): 4-13.

2. Vanderstappen I., *et al*. "The effect of prophylactic clonidine on postoperative shivering. A large prospective double-blind study". *Anaesthesia* 51.4 (1996): 351-355.

3. Ma H., *et al*. "The effect of clonidine on gastrointestinal side effects associated with ultra-rapid opioid detoxification". *Anesthesia and Analgesia* 96.5 (2003): 1409-1412.

4. Mikawa K., *et al*. "Oral clonidine premedication reduces vomiting in children after strabismus surgery". *Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie* 42.11 (1995): 977-981.

5. Apfel CC., *et al*. "A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers". *Anesthesiology* 91.3 (1999): 693-700.

6. Aldrete JA. "Post-anesthetic recovery score". *Journal of the American College of Surgeons* 205.5 (2007): e3-e5.

7. Palumbo P., *et al*. "Modified PADSS (Post Anaesthetic Discharge Scoring System) for monitoring outpatients discharge". *Annali Italiani di Chirurgia* 84.6 (2013): 661-665.

8. Apfel CC., *et al*. "Comparison of predictive models for postoperative nausea and vomiting". *British Journal of Anaesthesia* 88.2 (2002): 234-240.

9. Koivuranta M., *et al*. "A survey of postoperative nausea and vomiting". *Anaesthesia* 52.5 (1997): 443-449.

10. Baptista JF., *et al*. "Epidural anesthesia with ropivacaine with or without clonidine and postoperative pain in hemorrhoidectomies". *Acta Cirurgica Brasileira/Sociedade Brasileira para Desenvolvimento Pesquisa em Cirurgia* 29.3 (2014): 201-208.

11. Boogmans T., *et al*. "Epidural neostigmine and clonidine improves the quality of combined spinal epidural analgesia in labour: a randomised, double-blind controlled trial". *European Journal of Anaesthesiology* 31.4 (2014): 190-196.

12. Bohrer H., *et al*. "Clonidine as a sedative adjunct in intensive care". *Intensive Care Medicine* 16.4 (1990): 265-266.

13. Baumgartner GR and Rowen RC. "Transdermal clonidine versus chlordiazepoxide in alcohol withdrawal: a randomized, controlled clinical trial". *Southern Medical Journal* 84.3 (1991): 312-321.

14. Kobayashi N and Ishii S. "[Effectiveness of clonidine in postoperative nausea and vomiting--epidural versus oral administration]". *Masui The Japanese Journal of Anesthesiology* 46.4 (1997): 538-542.

15. Buchman AL., *et al*. "Clonidine reduces diarrhea and sodium loss in patients with proximal jejunostomy: a controlled study". *JPEN Journal of Parenteral and Enteral Nutrition* 30.6 (2006): 487-491.

16. Lin SK., *et al*. "A double-blind, placebo-controlled trial of dextromethorphan combined with clonidine in the treatment of heroin withdrawal". *Journal of Clinical Psychopharmacology* 34.4 (2014): 508-512.

17. Huilgol V., *et al*. "Acute effect of clonidine on gastric emptying in patients with diabetic gastropathy and controls". *Alimentary Pharmacology and Therapeutics* 16.5 (2002): 945-950.

18. Rosa-e-Silva L., *et al*. "Treatment of diabetic gastroparesis with oral clonidine". *Alimentary Pharmacology and Therapeutics* 9.2 (1995): 179-183.

19. Thumshirn M., *et al*. "Modulation of gastric sensory and motor functions by nitrergic and alpha2-adrenergic agents in humans". *Gastroenterology* 116.3 (1999): 573-585.

20. Lang IM and Sarna SK. "The role of adrenergic receptors in the initiation of vomiting and its gastrointestinal motor correlates". *The Journal of Pharmacology and Experimental Therapeutics* 263.1 (1992): 395-403.

21. Robichaud A., *et al*. "PDE4 inhibitors induce emesis in ferrets via a noradrenergic pathway". *Neuropharmacology* 40.2 (2001): 262-269.

22. Oddby-Muhrbeck E., *et al*. "Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery". *Anesthesiology* 96.5 (2002): 1109-1114.

23. Maina A., *et al*. "Transdermal clonidine in the treatment of severe hyperemesis. A pilot randomised control trial: CLONEMESI". *BJOG: An International Journal of Obstetrics and Gynaecology* 121.12 (2014): 1556-1562.

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