

Dexmedetomidine-based Total Endovenous Anesthesia in Radical Surgery for Breast Cancer. An observational case series study involving 10 patients

Research Article

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Abstract

Introduction: Ambulatory treatment of breast cancer is limited by vomiting and post-operative pain, and general anesthesia is implicated in these effects. Dexmedetomidine supplies analgesia and sedation without respiratory depression when it is administered intravenously. We demonstrate the usefulness of Dexmedetomidine as a general endovenous anesthesia.

Methods: Female patients were included with ages ranging between 42 and 83 years old and with a breast cancer diagnosis. They were scheduled for radical surgery between May 2009 and April 2011. Dexmedetomidine plus Propofol and Fentanyl were administered. Intra-operative monitoring included electrocardiography, arterial blood gas analysis, blood pressure, heart rate, respiratory rate, and arterial oxygen saturation. We registered surgery and sedation according to the bispectral index and Ramsay scales.

Results: The patients were maintained with 95% oxygen saturation and breathed spontaneously during the entire procedure with supplementary oxygen. Their blood pressure remained constant; heart rate showed only a mild reduction, bispectral index was maintained at 50, and the Ramsey scale-at IV. The infusion was discontinued without the patients experiencing dizziness or vomiting; the patients had an easy response-to-voice awakening and remained in the recovery room for at least 2 h. They were physiologically stable, and were left with additional supplementary oxygen. There was no pain or agitation observed during the recovery period and no narcotic was administered.

Conclusion: Dexmedetomidine is a useful intravenous anesthetic agent in procedures such as radical breast surgery, with faster recovery and residual analgesia.

KeyWords: General Anesthesia; Intravenous Anesthetics; Dexmedetomidine; Breast Cancer.

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Introduction

In the U.S, cancer is the second most common cause of death (one of every four deaths), only surpassed by cardiac disease [1]. The most frequent cancer in women is breast cancer and it is estimated that 30 - 40% of patients with breast cancer will die of metastatic disease [2]. Due to the high number of patients annually hospitalized for surgical treatment of breast cancer, efforts

have been focused on reducing hospital costs and hospital stay time [3]. Breast surgery as an ambulatory procedure, however, has been limited because of the presence of nausea, vomiting, and post-operative pain. General anesthesia can be primarily implicated in these effects and its emetic properties have the highest incidence in women, particularly in patients with breast surgery [4].

Dexmedetomidine (Precedex; Hospira, Inc., Lake Forest, IL, USA) is a selective α_2 adrenoceptor agonist with unique properties. Dexmedetomidine (DEX) provides analgesia and sedation without respiratory depression when it is administered intravenously (i.v.) [5,6]. The U.S. Food and Drug Administration have approved DEX for procedural sedation in non-intubated patients and the approved dose for continuous i.v. sedation in intensive therapy in patients who are mechanically ventilated is a bolus of DEX (1 $\mu\text{g}/\text{kg}$) for administration in 10 min, followed by an infusion of 0.2–0.7 $\mu\text{g}/\text{kg}/\text{h}$ [7]. Indications for DEX include pre-medication and as an adjuvant for general and regional anesthesia, with a sedative and analgesic effect. DEX has been employed as base anesthesia or unique anesthesia in short procedures as indicated by endoscopic studies, difficult upper airways surgeries, or in patients with morbid obesity [6], even at doses of 5–10 $\mu\text{g}/\text{kg}/\text{h}$ [5]. At excessive doses, DEX does not cause significant hemodynamic or respiratory adverse effects. Higher i.v. infusion has been described without harmful effects [5].

The objective of the present work is to report our experience in the management of radical breast cancer surgery with DEX in a series of patients.

Case Series

Ten non-smoker female patients diagnosed with breast cancer, regardless of age and clinical stage, scheduled to undergo radical breast surgery were included. The Institutional Ethics Committee approved the study; all patients gave written informed consent. The inclusion/exclusion criteria are depicted in table 1.

Mean age of the patients was 54.6 years (range 42 to 83 years). History was unremarkable for previous surgeries and for treatments with analgesics; there was no need to take analgesics 30 days prior to surgery. Pre-operative diagnosis included ductal carcinoma (eight patients) and lobular carcinoma (two patients). The clinico-pathological characteristics of the patients are depicted in table 2.

Patients presented on the same day of their surgery. Intervention type was mastectomy in seven cases and quadrantectomy in the remaining three; all but three underwent a short-stay ambulatory surgery. The mean duration of surgical procedures was 135 min (range, 60–195 min) and no intra-operative complications were registered. Histopathological examination revealed negative margins on all of the mastectomy and quadrantectomy specimens.

Anesthetic procedure

In the pre-anesthetic care unit and after obtaining baseline meas-

urement of heart rate (HR), respiratory rate (RR) and blood pressure (BP), DEX was started with a pre-induction dose of 1 µg/kg/min by continuous i.v. infusion for 15 min immediately prior to breast surgery. The pre-induction doses were then followed by DEX infusion at 0.4 µg/kg/h. This resulted in conscious sedation without respiratory or cardiovascular compromise (Ramsay III/IV). Induction of anesthesia was performed using DEX, propofol (1 mg/kg⁻¹), and fentanyl (2 µg/kg/h) without the need for endotracheal intubation, with the patients spontaneously breathing throughout the procedure (oxygen saturation at >95%); the patient dozed, with easy response to the voice and integral consciousness. Intraoperatively, the anesthesia was maintained with DEX infusion at 0.5–0.7 µg/kg/h and, by an alternative intravenous route, propofol (1 µg/kg/min). Supplementary analgesia was achieved by administering fentanyl. Intraoperative sedation scoring was done every 10 minutes. The BIS index values between 40 and 60 indicated general anesthesia. When the patients were sedated (Ramsay IV, BIS 60), we proceeded to the radical mastectomy or quadrantectomy. The average DEX dose used was 200 ± 50 µg (0.3 - 0.5 µ/kg/min). Of note, BP was usually maintained with no significant variations during the whole procedure (table 3) and no significant changes or fluctuations were observed in HR. The BIS was maintained at 50 (range 42 to 64) and the Ramsay level was maintained at IV during the entire procedure.

At the end of the surgical procedure, propofol and DEX infusions were discontinued with patients spontaneously breathing without dizziness, nausea, or vomiting; therefore, there was no need for postoperative nausea and vomiting management. Ketorolac, (if requested by patient) was the endovenous postoperative analgesics administered in the post-anesthetic care unit (PACU). Patients recovered were maintained for at least 2 h. They were asked to rate

Table 1. The inclusion/exclusion criteria.

Inclusion criteria	
For ambulatory surgery	- American Society of Anesthesiologists (ASA) class 1 and 2 females
	- Adult responsible for the patient postoperatively
	- Home telephone or in the neighborhood
For conservative surgery	- Tumor size less than 3 cm
	- Have not received chemotherapy and/or radiation therapy previously
	- Tumor-breast volume ratio less than 1:5, axillary nodal status N0 - N1a/b
Exclusion criteria	- ASA 3 or greater
	- Absence of a patient's responsible adult
	- Inability to understand and follow outpatient procedure care
	- Carcinoma in situ or multicentric disease
	- Morbid obesity
	- Illicit drug user
	- History of malignant hyperthermia
	- Collagen vascular disease
	- Prior chemotherapy or radiation therapy
	- Prior axillary surgery or nodal status greater than N1b
	- Pregnancy or lactation
	- Locally advanced (T3 - 4) or metastatic tumor
	- Large tumor/breast ratio
- Central tumor	
- Patient refusal to participate	

Table 2. Intravenous total anesthesia in radical surgery for breast cancer. Demographic characteristics of patients.

Patient	Age (yr)	Sex	Weight (Kg)	Histology type	Operation
1	44	female	59	Lobular	ARM
2	42	female	66	Ductal	AQA
3	75	female	65	Lobular	ARM
4	57	female	64	Ductal	IRM
5	47	female	56	Ductal	ARM
6	43	female	58	Ductal	ARM
7	83	female	68	Ductal	AQA
8	52	female	59	Ductal	IRM
9	57	female	60	Ductal	AQA
10	46	female	63	Ductal	IRM

Keys and Abbreviations: ARM = Ambulatory radical mastectomy; AQA = Ambulatory quadrantectomy plus axillary lymph node dissection; IRM = Inpatient radical mastectomy;

Table 3. Intravenous total anesthesia in radical surgery for breast cancer. Distribution of clinical data, hemodynamic values, and the intra-operative evaluation of patients.

Patient	systolic BP*	diastolic BP*	Heart Rate*	Breath Rate*	SaO2	BIS*	Ramsay	Duration
1	112.5±9.8	58.4±7.0	57.4±3.3	10.8±1.10	>95%	49.3±5.5	IV	160 min
2	100.2±11.8	62.3±6.2	60.1±4.2	12.9±1.09	>95%	56.1±4.2	IV	60 min
3	110.7±13.4	60.4±3.3	58.3±3.9	11.7±1.02	>95%	52.1±3.4	IV	150 min
4	113.9±14.9	63.5±7.1	57.8±3.0	12.6±1.23	>95%	51.06±5.02	IV	165 min
5	110.1±8.9	59.2±4.2	56.3±4.1	11.6±1.02	>95%	60.0±3.2	IV	150 min
6	100.9±11.9	60.4±3.1	57.5±3.7	10.5±1.68	>95%	58.0±4.4	IV	160 min
7	108.3±13.9	59.8±4.4	56.9±4.2	12.6±1.35	>95%	59.0±5.0	IV	70 min
8	100.3±11.4	56.6±6.1	59.4±3.6	10.4±1.05	>95%	57.04±2.1	IV	195 min
9	113.4±10.9	60.5±3.2	60.6±4.2	12.8±1.80	>95%	49.06±6.2	IV	70 min
10	110.3±11.7	62.2±5.4	60.9±3.8	12.7±1.02	>95%	55.05±5.8	IV	170 min

* Measure (mean ± SD).

Keys and Abbreviations: BIS = BIS index; BP = Blood pressure; SaO2 = Oxygen saturation.

their pain on a 0 to 10 numeric rating scale, with 0 representing "no pain" and 10 "the worst possible pain"; average pain was 0/10 at 1 h and 2/10 at 3 h, when the patients were discharged from PACU. An oral antibiotic was indicated (Cephalexin, 500 mg four times daily) for 5 days and oral Ketorolac in case of need. Patients scheduled for ambulatory surgery were discharged from the hospital after a PACU stay of approximately 3 h.

Statistical Analyses

Variables are expressed in terms of the mean and standard deviation. The Kolmogorov–Smirnov test was used to test the normal distribution of data. Comparisons of ordered data were performed by the Wilcoxon–Mann–Whitney test. Categorical data were analyzed by the Fisher's exact test. Serial measurements and changes in the vital measurements from baseline were analyzed by using one-way analysis of variance (ANOVA). Significance was expressed by P-values. P-values < 0.05 were considered statistically significant.

Discussion

The sedative effect of DEX is similar to that of natural sleep; subjects under sedation with DEX awaken easily on their being stimulated and return to the sedation state rapidly. Superficial sedation with easy awakening employing DEX is preferable for certain patients due to the lack of respiratory depression. Similarly, some of the accompanying effects (low BP, diminution of HR, dryness of mucosas) can, in certain cases, be of clinical usefulness. Recovery time with DEX is comparable with other anesthesia types, but with softer emersion without the need of a narcotic [10]. Adding a small dose of Propofol i.v. to the DEX aids in achieving better surgical conditions and diminishes the doses of both drugs necessary for obtaining an optimal surgical state.

The analgesic effect of DEX has also been reported as a main parameter during monitored anesthetic care and after major surgical procedures [11-13]. Administration of DEX prior to the end of a major surgical procedure associated with post-operative pain reduced the early post-operative need for morphine by 66%; additional analgesia is not needed in the first hour of recovery [14]. Other groups [15-17] have already reported the use of intraoperative DEX infusion in laparoscopic bariatric surgery and supratentorial craniotomies but followed by tracheal intubation, different from our procedure with no patient necessitating in-

sive respiratory support.

Conventional sedation point systems based on clinical observations may not work well with DEX-induced sedation [8]. The Ramsay scale (Ramsay Sedation Score) is characterized by significant interobserver variability [9]. The BIS is a number derived from the bispectral analysis of the EEG that provides information on the interactions between the cortical and subcortical area that change under the influence of sedatives and hypnotics [9]. Conscious sedation corresponds to a BIS index of 70 - 80 and general anesthesia is reflected by a BIS index within the range of 40 - 60 [9]. BIS values were approximately 20 points lower with DEX-induced sedation than with that induced by propofol [8]. Thus, BIS is considered very useful monitoring in these cases.

Some patients with breast cancer will carry micrometastasis up to the moment of the procedure. There are peri-operative period factors that can result in immunosuppression, promoting metastatic development [18]. The surgical act, then, can lead to the releasing of malignant cells within the blood and lymph node systems. This dissemination can become manifested with local and distant recurrences of the patient's immunocompetence. It has been postulated that there can be a "decisive period" during which the microscopic disease cannot be controlled and it can remain during the development of recurrences. The recurrence of certain anesthetics can then be a factor for the success or failure in the control of this microscopic disease [19,20].

Propofol has to be combined with an opioid when it is utilized in total intravenous anesthesia and opioids possess various actions that can cause the dissemination of malignant cells [21,22]. Opioids suppress post-operative cytotoxicity in NK lymphocytes in humans [23]. In addition, opioids stimulate angiogenesis and tumor progression, in part via activating cyclooxygenase-2 and increasing the production of prostaglandin E2 [24]. In addition to diminishing the requirements of the anesthetic and opioid agents, DEX hypothetically could reduce the recurrence risk in breast cancer [25,26], via the α_2 adrenergic effect on human mammary cells [27] as a significant increase in mammary tumor growth induced by clonidine in mouse have been described [28]. There is evidence that post-operative pain is an important mediator of the tumor promoter effects of surgery [29]; by extending post-operative anesthesia, DEX can attenuate the negative impact of post-operative pain. Patient outcomes in our study were characteristically associated with low postoperative pain scores, low PONV rates and short PACU lengths of stay; however, the primary outcomes of interest were neither the incidence of PONV nor the length of PACU stay. Moreover, no consideration was done on patients' satisfaction using this technique.

In the decade of the eighties, 46.9 of the 117,982 patients submitted to mastectomy in the U.S. remained hospitalized for 6 or more days after the procedure and in 1995, 10.8% of mastectomies were ambulatory [30]. Since 1998, the routine use has been proposed of Ambulatory radical surgery (ARS) in breast cancer [31]. While only a modest increase (3 - 3.5%) in the proportion of readmitted patients [30], performing (ARS) has not been adopted in routine fashion, which would afford economic incentives, because this can result in substantial savings of means in times of economic crisis.

The technique used here is novel, with spontaneous breathing, on an outpatient basis and with no hemodynamic or respiratory complications. Several advantages of this technique have been observed: reduced requirements for intraoperative propofol and

- fentanyl; there was no need for tracheal intubation and use of muscle relaxants; recovery time was comparable with that of other anesthesia types, but with softer emergence with DEX; a good 24-hour control of postoperative pain was achieved with lower requirements for analgesic support.

Limitations of this study

The main limitation of our study was the small number of cases. The fact that only 10 patients were studied makes it underpowered and difficult to make a conclusion on whether dexmedetomidine actually helped these patients. Nevertheless, we believe that this method is promising. Our preliminary results are encouraging and further studies are desirable.

Conclusion

DEX is a useful anesthetic/analgesic not only as an adjuvant to anesthesia, but also as a unique anesthetic agent, for short procedures including difficult endoscopic procedures, surgery on upper airways obese patients, as well as for major procedures such as radical and extensive surgeries for cancer with an important shortening of the recovery period and affording the opportunity of performing ambulatory radical surgery for breast cancer, which has been attempted for two decades [32].

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