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Original Article

Pre-emptive dexmedetomidine decreases the incidence of chronic post hysterectomy pain

Chao Han[1,2], Daoyun Lei[1,2], Wenjie Jiang[1,2], Hongfei Ren[1,2], Guangyuan Su[1,2], Shunhua Feng[1,2], Zhijun Ge[1,2], Tieliang Ma[1,2]

[1]The Affiliated Yixing Hospital of Jiangsu University, Yixing, Jiangsu, P.R. China; [2]Yixing Clinical College, Medical College of Yangzhou University, Yixing, Jiangsu, P.R. China

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Abstract: Background: Chronic post hysterectomy pain (CPHP) is pain that recurs or persists for at least two months following surgery. Objectives: The goal of this study was to determine the effect of pre-emptive dexmedetomidine (Dex) on the incidence of CPHP in patients undergoing abdominal hysterectomy under general anesthesia. Patients and Methods: Eighty eligible elective abdominal hysterectomy patients were randomly divided in two groups of 40 each. The Dex group received 0.5 μg/kg/hour of dexmedetomidine infusion from 15 minutes prior to initiation of anesthesia until peritoneum closure, while the control (Con) group received a corresponding volume of 0.9% saline. Both groups were administered standard general anesthesia with routine monitoring. After 2, 6, 12 months, patients were recalled to pain clinic to assess the presence of pain. Results: Thirty-six patients in the Dex group and thirty three in the Con group completed all follow-ups. The demographic characteristics were not significantly different between the two groups ($P > 0.05$). The incidence of CPHP in postoperative 2, 6, and 12 months were 13.9%, 5.6%, 2.8% in the Dex group were significantly lower than 30.3%, 24.2%, 18.2% in the Con group, respectively ($P < 0.05$). Conclusions: Pre-emptive administration of dexmedetomidine may decrease the incidence of CPHP, suggesting a preventive effect of dexmedetomidine on chronic post-surgical pain.

Keywords: Dexmedetomidine, CPHP, postoperative

Induction

Chronic post hysterectomy pain (CPHP) is defined as persistent or intermittent pain developed after a surgical procedure for at least 2 months, excluding the pain derived from other causes or pre-existing pain [1, 2]. The incidence rates of CPHP in different literatures range from 5 to 50% and the variability might be due to different study designs and methodologies, and diagnostic criteria used. Our previous study has showed that 28% of patients after hysterectomy experienced CPHP and most of them reported a mild pain and minimal interfere with daily activities expect for the disorder of mood and sleep [3]. Furthermore, intra-operative dexmedetomidine was associated with a decreased incidence rate of CPHP.

Dexmedetomidine is a highly selective alpha-2-drenoreceptor agonist that exerts sedative, analgesic, and sympatholytic properties [4]. Several studies have verified that intra-operative administration of dexmedetomidine could reduce postoperative acute pain after hysterectomy [5, 6]. However, there is currently no literature published about the effect of dexmedetomedine on CPHP, although a recent study suggested that pre-emptive dexmedetomidine could decrease the incidence of post-thoracotomy pain syndrome in patients undergoing coronary artery bypass grafting [7].

This prospective, double-blind, randomized, placebo-controlled study was conducted to assess the effects of pre-emptive dexmedetomidine on chronic post-surgical pain in patients undergoing abdominal hysterectomy under general anesthesia.

Materials and methods

Ethics declaration

The study was approved by the Ethics Committee of the Affiliated Yixing Hospital of Jiangsu University, China and all patients gave written informed consent.

Patient selection

From April to December 2016, 80 consecutive patients, aged 18 to 80 years, of American Society of Anesthesiologists (ASA) physical classification classes I-III, scheduled for elective abdominal hysterectomy under general anesthesia for benign indications (leiomyoma, menorrhagia or metrorrhagia) at the Department of Gynecology, Affiliated Yixing Hospital of Jiangsu University were prospectively invited to participate in this study. Exclusion criteria were known allergy to dexmedetomedine, clinically significant cardiovascular or central nervous system disease, impaired renal or hepatic function, known history of second or third degree heart block, severe bradycardia (< 55 bpm), presence of pre-surgical pain, cognitive impairment, previous prescription of analgesic treatment, anxiety or depression (> 8 using Hospital Anxiety and Depression Scale (HADS) in a Chinese version), or drug abuse. Patients with indications for uterine prolapse, endometriosis, malignant disease, pelvic pain or inability to finish trail were also excluded. The patients were randomly assigned into two groups each of 40 using a computer-generated randomization scheme: a dexmedetomedine (Dex) group and a control (Con) group.

Anesthesia and analgesia procedures

Patients were not given any premedication. Standard monitors including pulse oximetry, electrocardiogram, noninvasive arterial blood pressure, and bispectral index (BIS) electrodes were applied. In the Dex group, 0.5 μg/kg/hour of dexmedetomidine was infused by a microinjection pump from 15 minutes prior to the initiation of anesthesia until peritoneum closure. In the Con group, patients received a corresponding volume of 0.9% saline. General intravenous anesthesia was induced with midazolam (0.3 mg/kg), etomidate 0.3 mg/kg, fentanyl (5 μg/kg) and vecuronium (0.15 mg/kg). All patients were intubated and mechanically ventilated with 100% oxygen, VT 8-10 mL/kg, frequency 10-14/min, with an end-tidal CO_2 of 30-40 mmHg during surgery procedure. Propofol 4-12 mg/kg/h and remifentanil 15-40 μg/kg/h were infused by micro pumps to maintain anesthesia, with the concentration titrated to hemodynamics stability and enough depth of anesthesia (BIS value between 40 and 60). Intermittent administration of vecuronium (0.075 mg/kg) was used to keep muscle relaxation as required.

After the surgery, patients were transferred to PACU and monitored per institutional PACU protocol. Atropine (0.5 mg) and neostigmine (1 mg) were used to reverse muscle relaxation. Patients were extubated after adequate recovery as was judged by the anesthesiologist at PACU. Rescue analgesia was provided with tramadol 50 mg intravenous if the patient's numerical rating scale (NRS) pain score (0 = no pain; 10 = worst imaginable) was > 3. Before discharge to ward, all patients were received patient-controlled intravenous analgesia (PCIA) using an analgesia pump filled with sufentanil 20 μg/kg, tropisetron 5 mg, diluted to 100 mL with 0.9% normal saline. It was programmed to give 2 mL/h background infusion with a 10-μg bolus of sufentanil solution, with a 5-min lockout time.

Peri-operative data collection

Peri-operative vital signs, dose of anesthetics, and rescue tramadol were collected from hospital database. NRS, sufentanil dose by PCIA and adverse reactions were recorded at 2, 6, 12, 24 and 48 hours after the surgery by a specified anesthesiologist blinded to group allocation.

Chronic pain assessments

Chronic pain assessments were conducted in pain clinic at 2, 6, and 12 months after hysterectomy and patients were informed by telephone contact. Another anesthesiologist made the diagnosis according to the definition of CPHP. If diagnosed of CPHP, a douleur neuropathic 4-questionnaire (DN-4) was followed to ascertain whether the pain was a neuropathic Pain (NP).

Statistical analysis

Statistical analysis was performed using the SPSS16.0 software package with $P < 0.05$ considered statistically significant. The results are expressed as mean ± standard deviation or median (range) for continuous variables and as percentage for categorical variables. Chi-square and Mann-Whitney U tests were performed for categorical and continuous variable analyses.

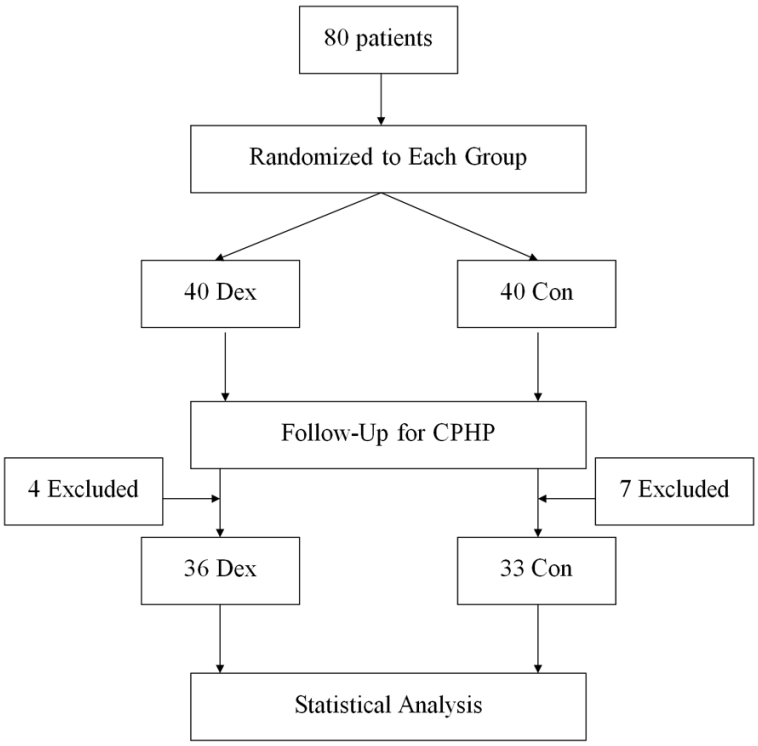

Figure 1. Flow Diagram of the Study. The entire procedure of the trial is illustrated, including randomization of patients, follow-up, and final analysis.

Results

All patients passed the peri-operative period steadily with NRS below 3. No significant adverse reactions were observed. Four patients in the Dex group and seven in the Con group did not complete all follow-ups, despite multiple phone call attempts. Therefore, 69 patients, 36 in the Dex group and 33 in the Con group were analyzed (**Figure 1**). **Table 1** shows the demographic and clinical characteristics of the study. The age, body mass index (BMI), comorbidities, laparotomy history, duration of surgery, and blood loss were not significantly different between the two groups ($P > 0.05$). Consumption of intra-operative propofol and remifentanil, rescue tramadol, and PCIA sufentanil were significantly lower in Dex group compared with Con group ($P < 0.05$). **Table 2** summarizes the development of CPHP. The incidence of CPHP in postoperative 2, 6 and 12 months were 13.9%, 5.6%, 2.8% in Dex group were significantly lower than 30.3%, 24.2%, 18.2% in Con group, respectively ($P < 0.05$). There were significant differences in the incidence of NP at 6 and 12 months ($P < 0.05$), but not at 2 months ($P > 0.05$).

Discussion

In the present study, pre-emptive dexmedetomidine was found to decrease the incidence of CPHP in the patients undergoing abdominal hysterectomy under general anesthesia. The reported incidence of CPHP in the Con group was close to previous studies [3, 8].

Development of CPHP is a complex process which involves biologic, psychosocial, and environmental mechanisms that have yet to be incompletely understood. Similar with other surgeries, the underlying mechanism of chronic pain following hysterectomy includes: 1) peripheral sensitization; 2) central sensitization at spinal and supraspinal sites innervating the injured area; 3) inhibition of descending modulation [9]. Understanding the mechanisms for development of CPHP is crucial in establishing better prevention strategies.

Surgery-induced inflammatory mediators including cytokines, bradykinin, and prostaglandins are released from injured and inflammatory cells at the site of tissue damage. With ongoing nociceptive input, nociceptors demonstrate reversible plasticity in response to inflammatory mediators, result to peripheral and central sensitization [9]. Pre-emptive analgesia, which pharmacological interventions performed prior to surgery may attenuate, may weaken the post-operative pain through prevention and inhibition of central sensitization induced by inflammatory mediators [10]. A Meta-analysis of 12 randomized controlled trials (RCTs) revealed that dexmedetomidine significantly suppresses pro-inflammatory cytokine production dose-dependently during surgical procedures [11]. The finding may explain the lower incidence rate of CPHP in the Dex group.

The descending pathways projecting from cerebral structures to the dorsal horn of the spinal cord plays a complex and crucial role in the

Table 1. Demographic and clinical characteristics of the objective

Variable	Dexmedetomidine (n=36)	Control (n=33)	*P* Value
Age (y)	52.7±8.4	50.9±7.0	0.33
BMI (kg/m^2)	23.6±2.3	24.5±2.5	0.12
HTN	9	10	0.31
DM	4	3	0.39
ASA score			0.59
I	21	17	
II	12	13	
III	3	3	
Laparotomy History	7	5	
Duration of Surgery (min)	70.4±10.4	70.8±12.9	0.88
Blood loss (ml)	157.2±35.2	149.1±40.7	0.37
Propofol (mg)	536.1±88.9	634.2±104.4	< 0.001
Remifentanil (μg)	27.4±5.4	36.4±6.0	< 0.001
Tramadol (mg)	11.1±20.7	22.7±24.9	0.03
Sufentanil (μg)	57.4±4.8	65.1±7.1	< 0.001

Table 2. Development of CPHP

		Dexmedetomidine (n=36)	Control (n=33)	*P* Value
2 months	CPHP	5	10	0.049
	NP	2	5	0.09
6 months	CPHP	2	8	0.01
	NP	0	4	0.02
12 months	CPHP	1	6	0.02
	NP	0	4	0.02

development for CPHP [12]. It is widely accepted that chronic pain associated with central sensitization is subject to abnormal, imbalanced descending modulation: enhanced descending facilitation and weakened descending inhibition. You et al. [10] reported that dexmedetomidine could significantly enhance descending inhibition and/or decrease descending facilitation, which further confirm the role of dexmedetomidine in preventing CPHP.

Several researches and our previous study have showed that approximate 50 percent of patients with CPHP report a neuropathic pain (NP) characterized by spontaneous pain, increased responsiveness to painful stimuli and pain perceived in response to normally non-noxious stimuli [3, 8, 13]. Similarly, the incidence of NP in present study at 2, 6, and 12 months after hysterectomy is 50%, 50% and 66.7% respectively. The noradrenergic system plays a pivotal role in the development of NP and α2 adrenoceptor subtype modulation as strategy for neuropathic pain relief has received increased attention [14]. The underlying mechanism of dexmedetomidine alleviated NP includes: 1) acting on presynaptic sites to reduce noxious stimuli-induced excitatory postsynaptic potential (EPSCs) and on postsynaptic substantia gelatinosa (SG) neurones to induce an outward current by G-protein-mediated activation of K^+ channels [10], 2) increasing acetylcholine concentrations in the spinal dorsal horn [15], 3) decreasing release of the neuropeptides such as CGRP and Substance P [12, 16]. Furthermore, the exaggerated sympathetic nervous system contributes to the pathophysiology and clinical presentation of NP [17]. Dexmedetomidine has sympatholytic properties, which may explain the lower incidence of NP in the Dex group.

There are four important limitations to this study. First, the sample size was not determined to assess the effect of dexmedetomidine on CPHP. Second, the study relied on subjective self-reporting, which might be influenced by the psychological and mental status of patients. It is also worth mentioning that there was a 14% dropout during the follow-up, which could impact the accuracy of the results. Finally, the effects of different doses of dexmedetomidine on the development for CPHP were not explored. Despite these limitations, the merits of the study include the prospective design and homogenization of research object.

In conclusion, pre-emptive administration of dexmedetomidine was associated with a decreased incidence of CPHP. These findings suggest a protective effect of dexmedetomidine for CPHP in abdominal hysterectomy patients. Further study is needed to determine optimal dose.

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Disclosure of conflict of interest

None.

Address correspondence to: Tieliang Ma, The Affiliated Yixing Hospital of Jiangsu University, 75 Tongzhenguan Road, Yixing 214200, Jiangsu, P.R. China. Tel: 86-510-87921196; Fax: 86-510-87921110; E-mail: matieliang@foxmail.com

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