

# Lidocaine-prilocaine Cream Combined with Rapid Induction Creates Excellent Anaesthesia for Ovarian Cystectomy: A Prospective, Randomized, Controlled, Double-blinded Study

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## ABSTRACT

**Objective:** To develop a highly painless and effective form of anaesthesia for ovarian cystectomy.

**Methods:** Seventy-two ovarian cystectomy patients were recruited, from August 2012 to July 2015, from The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, China. They were randomly divided into the treatment group ( $n = 36$ ) and the control group ( $n = 36$ ) in a double-blinded prospective study. The patients in the control group were subjected to the regular rapid induction of anaesthesia, while those in the treatment group were treated with lidocaine-prilocaine cream (EMLA) 5 minutes ( $n = 6$ ), 10 minutes ( $n = 6$ ), 15 minutes ( $n = 6$ ), 20 minutes ( $n = 6$ ), 25 minutes ( $n = 6$ ) and 30 minutes ( $n = 6$ ) before surgery, respectively, combined with the rapid induction of anaesthesia (LCRIA). Then, the data obtained from the patients were recorded, including haemodynamic fluctuations, tube tolerance time, sore throat and throat discomfort. During the procedure, all the patients were told to score the pain intensity according to the visual analogue scale (VAS) as described.

**Results:** When extubation was performed, the diastolic blood pressure ( $68.53 \pm 5.64$  mmHg versus  $74.43 \pm 5.82$  mmHg), systolic blood pressure ( $112.43 \pm 3.24$  mmHg versus  $123.04 \pm 5.32$  mmHg), mean arterial pressure ( $81.23 \pm 5.03$  mmHg versus  $86.43 \pm 5.54$  mmHg) and heart rate ( $87.43 \pm 4.54$  times/minute versus  $96.32 \pm 5.11$  times/minute) of the patients in the treatment group increased significantly ( $p < 0.05$ ), but were lower than those in the control group. The endotracheal tube tolerance time of the patients in the treatment group was significantly longer ( $p < 0.05$ ) than that of those in the control group ( $13.34 \pm 2.43$  minutes versus  $10.03 \pm 1.84$  minutes). The incidence of sore throat (5.41% versus 21.62%) and pharyngeal discomfort (8.11% versus 35.14%) in the treatment group was significantly lower ( $p < 0.05$ ) than that in the control group. When comparing the VAS pain scores, the patients who had been treated with lidocaine-prilocaine cream 20 minutes before the surgery ( $3.2 \pm 0.56$  minutes) suffered from significantly less pain ( $p < 0.05$ ) than those in the control group ( $5.6 \pm 1.74$  minutes), and the treatment group experienced the least pain.

**Conclusion:** The application of LCRIA can effectively reduce pain, relieve the haemodynamic fluctuations caused by extubation stress reaction during ovarian cystectomy, enhance tolerance to the endotracheal tube, and reduce the incidence of sore throat and pharyngeal discomfort.

**Keywords:** Lidocaine-prilocaine cream, ovarian cystectomy

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## La crema de lidocaína-prilocaina, combinada con inducción rápida crea una excelente anestesia para la cistectomía ovárica: un estudio prospectivo, aleatorio, controlado, doble ciego

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### RESUMEN

**Objetivo:** Desarrollar una forma de anestesia altamente eficaz y sin dolor para la cistectomía ovárica.

**Métodos:** Se reclutaron setenta y dos pacientes de cistectomía ovárica, de agosto de 2012 hasta julio de 2015, del Segundo Hospital Afiliado, Escuela de Medicina, Universidad de Xi'an Jiaotong, China. Se les dividió al azar en un grupo de tratamiento ( $n = 36$ ) y un grupo control ( $n = 36$ ) de un estudio prospectivo doble ciego. Los pacientes en el grupo control fueron sometidos a la regular rápida inducción de la anestesia, mientras que los del grupo de tratamiento fueron tratados con crema de lidocaína y prilocaína (EMLA) durante cinco minutos ( $n = 6$ ), 10 minutos ( $n = 6$ ), 15 minutos ( $n = 6$ ), 20 minutos ( $n = 6$ ), 25 minutos ( $n = 6$ ) y 30 minutos ( $n = 6$ ) antes de la cirugía, combinada con la rápida inducción de la anestesia (LCRIA). Entonces se registraron los datos obtenidos de los pacientes, incluyendo fluctuaciones hemodinámicas, tiempo de tolerancia a la intubación, dolor de garganta, y malestar de garganta. Durante el procedimientos, a todos los pacientes se les pidió dar una puntuación de la intensidad del dolor de acuerdo con la escala visual analógica (EVA).

**Resultados:** Cuando se realizó la extubación, los valores de la presión arterial diastólica ( $68.53 \pm 5.64$  mmHg versus  $74.43 \pm 5.82$  mmHg), la presión arterial sistólica ( $112.43 \pm 3.24$  mmHg versus  $123.04$  mmHg  $\pm 5.32$ ), la presión arterial media ( $81.23 \pm 5.03$  mmHg versus  $86.43$  mmHg  $\pm 5.54$ ), y la frecuencia cardíaca ( $87.43 \pm 4.54$  veces/min versus  $96.32 \pm 5.11$  veces/minuto) de los pacientes en el grupo de tratamiento aumentaron significativamente ( $p < 0.05$ ), pero estuvieron por debajo de los del grupo de control. El tiempo de tolerancia de intubación endotraqueal de los pacientes en el grupo de tratamiento, fue significativamente mayor ( $p < 0.05$ ) que el de los del grupo de control ( $13.34 \pm 2.43$  minutos versus  $10.03 \pm 1.84$ ). La incidencia del dolor de garganta (5.41% versus 21.62%) y la incidencia de molestias faríngeas (8.11% versus 35.14%) en el grupo de tratamiento, fue significativamente inferior ( $p < 0.05$ ) a la del grupo de control. Al comparar las puntuaciones de dolor en la escala EVA, los pacientes con crema de lidocaína-prilocaína 20 minutos antes de la cirugía ( $3.2 \pm 0.56$  minutos) sufrieron significativamente menos dolor ( $p < 0.05$ ) que los del grupo de control ( $5.6 \pm 1.74$  minutos), y el menor dolor correspondió al grupo de tratamiento.

**Conclusión:** La aplicación de LCRIA puede ser efectiva para reducir el dolor, aliviar las fluctuaciones hemodinámicas causadas por la reacción de estrés de extubación durante la cistectomía ovárica, mejorar la tolerancia al tubo endotraqueal, y reducir la incidencia de dolor de garganta y las molestias faríngeas.

**Palabras claves:** Crema de lidocaína-prilocaína, cistectomía ovárica

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### INTRODUCTION

Rapid induction with tracheal intubation and slow induction of anaesthesia are the most common methods in clinical anaesthesia induction (1, 2). Different

interventional methods for patients bring about different effects in the recovery period after surgery. Then, in the post-operative recovery period, patients treated with the above anaesthesia induction methods would suffer

from the stimulation of tracheal catheter, which induces adverse reactions like coughing, increased blood pressure and heart rate, and other severe complications, such as cardiovascular accident and respiratory tract spasm (3).

In recent years, lidocaine-prilocaine cream has been widely investigated in clinical anaesthesia induction (4). Lidocaine-prilocaine cream is one of the moderate anaesthetics, which is easily absorbed through the injured skin, mucosa and gastrointestinal tract (5). The superficial anaesthetic lidocaine-prilocaine cream mainly comprises prilocaine and lidocaine, which can block the ion beam generated by nerve impulses and conduction. The blocking effect will stabilize the nerve cells and play a local anaesthetic role. When used on the surface of mucosal or unbroken skin, it can release the prilocaine and lidocaine to the cortex and subcutaneous layer (6).

Prilocaine and lidocaine would accumulate in the nerve endings and cortical pain receptors, then act as cortical anaesthesia and eliminate pain (6). In addition, it also relieves post-operative pain and effectively alleviates the haemodynamics fluctuation in patients with extubation stress. Arnau *et al* have suggested that topical application of lidocaine-prilocaine cream 10 minutes before performing hysterosalpingography significantly ( $p < 0.05$ ) reduced pain during cervical manipulation with tenaculum and cannula and during cervical traction (7). Tavakolian *et al* have suggested that topical application of lidocaine-prilocaine cream as a topical anaesthetic on the cervix before the insertion of an intrauterine device (IUD) significantly reduced pain ( $p < 0.05$ ) during the IUD insertion, compared with the application of a placebo (5). Related studies have shown that lidocaine-prilocaine cream is safe and is an effective local anaesthetic agent that can be easily accepted by patients (8).

Ovarian cystectomy, the first-line treatment for benign ovarian tumours (9), is generally performed in conjunction with intravenous fentanyl analgesia or

patient-controlled epidural analgesia (10). However, few studies were involved in the promotion of clinical anaesthesia for ovarian cystectomy. Therefore, our study was aimed at investigating the anaesthetic effect of lidocaine-prilocaine cream combined with the rapid induction of anaesthesia (LCRIA) in ovarian cystectomy.

## SUBJECTS AND METHODS

### Clinical data

This study was approved by the Research Ethics Committee of The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, China. Seventy-two patients with ovarian cystectomy were recruited in this study from August 2012 to July 2015 from The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, after the exclusion of 12 patients (Table 1). The inclusion criteria used were: all the patients voluntarily participated in this study; they had no history of mental illness; and they all complied with our instructions. The exclusion criteria used were: all the patients with disturbance of consciousness, who could not be communicated with normally; patients with airway constriction, endocrine system diseases and/or cardiovascular diseases before the operation; patients involved in other research; patients with known hypersensitivity to local anaesthetics; and patients who had used oral analgesics before the procedure. Written consent was obtained, following explanations to the patients by a well-trained physician.

The blood oxygen saturation, pulse, heart rate, blood pressure, bispectral index and electrocardiogram of the patients had been routinely monitored. Radial artery puncture and cannulation were performed under local anaesthesia to monitor their arterial pressure. Peripheral venous pathway remained open, and oxygen by face mask was provided. The patients in the control group received routine induction of anaesthesia with intravenous injection of 0.5–1 mg/kg propofol, 0.02–0.06 mg/kg midazolam, 0.1 mg/kg vecuronium and 0.05–0.1

Table 1: General data of the two groups

Group	n	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )	JMS	Education		
							SMS	JC	BA
Treatment	36	36.04 ± 1.42	61.21 ± 3.21	154.43 ± 2.04	23.53 ± 2.03	6 (16.22)	11 (29.73)	12 (32.43)	8 (21.62)
Control	36	33.11 ± 1.32	57.43 ± 3.18	159.97 ± 2.03	23.61 ± 2.04	3 (8.11)	13 (35.14)	11 (29.73)	10 (27.03)
$t/\chi^2$		$t = 0.2196$	$t = 0.2962$	$t = 0.9723$	$t = 0.1691$	$\chi^2 = 1.4324$			
$p$		0.8268	0.7680	0.3342	0.8662	0.6980			

JMS: junior middle school; SMS: senior middle school; JC: junior college; BA: Bachelor's degree or above.

mg/kg fentanyl. After the endotracheal intubation, a ventilator was used for positive airway pressure treatment. Anaesthesia was maintained as follows: the fentanyl was kept pumping at the speed of 0.5 ug/kg/hour, then target-controlled infusion of propofol was used to preserve a concentration of 3 ug/mL. To keep the patients' muscles relaxed, additional vecuronium was used intermittently. Fentanyl pumping and propofol infusion were stopped 30 minutes and 10 minutes before the operation began, respectively.

The patients in the treatment group were treated with lidocaine-prilocaine cream purchased from Beijing Ziguang Pharmaceutical Co Ltd (batch number: 20140608). It was applied 5 minutes ( $n = 6$ ), 10 minutes ( $n = 6$ ), 15 minutes ( $n = 6$ ), 20 minutes ( $n = 6$ ), 25 minutes ( $n = 6$ ) and 30 minutes ( $n = 6$ ) before surgery, respectively, combined with rapid induction of anaesthesia. The lidocaine-prilocaine cream was smeared evenly in the range of 5 cm above the endotracheal cuff prior to the endotracheal intubation. Then a rapid-induced tracheal intubation was performed. After the successful intubation, the tube was connected to the anaesthesia machine for mechanical ventilation. The end-tidal partial pressure of carbon dioxide was maintained between 30 and 40 mmHg. The inhaled oxygen concentration was 100%; the inhaled oxygen flow was 1–2 L/minute; the tidal volume was 8–10 mL/kg; and the respiratory rate remained at 12/minute. For the maintenance of anaesthesia, the speed of intravenous infusion of remifentanyl and propofol was 8–12 ug/kg/hour and 2–4 ug/kg/hour, respectively. The process of general anaesthesia entailed the inhalation of 1% sevoflurane. The drugs were stopped after the completion of the operation. When the patients' autonomous respiration recovered with  $> 5$  mL/kg tidal volume and  $> 95\%$  oxygen saturation, an anaesthesia doctor, who did not know the grouping, was requested to extubate the patient, and relevant information was collected from the doctor.

### Observation index

Haemodynamic changes (diastolic blood pressure, systolic blood pressure, mean arterial pressure and heart rate) were recorded in the periods before anaesthesia and during extubation. From the drug's withdrawal to the extubation, the tube tolerance time was recorded. Then, after the extubation, the sore throat and throat discomfort were recorded.

During the procedure, all the patients were told to score the pain intensity according to the visual analogue scale (VAS) as described (11). The VAS included

a scaled 10 cm line (0–10: 0 = no pain and 10 = severe pain). The patients were instructed to specify the number which represented their level of perceived pain intensity. Explanations about the VAS were given to each patient before the procedure began.

### Statistical analysis

All the data were expressed as mean  $\pm$  standard deviation using SPSS 11.5. The data on haemodynamics were presented using the *t*-test. The throat discomfort in both groups of patients was presented using Chi-square test; and  $p < 0.05$  was considered as statistically significant.

## RESULTS

### Haemodynamic index before anaesthesia and during extubation

There was no significant difference ( $p < 0.05$ ) in the diastolic blood pressure, systolic blood pressure, mean arterial pressure and heart rate between the treatment and control groups before anaesthesia was administered. This indicated that the haemodynamic index of the patients was the same before anaesthesia was administered. The diastolic and systolic blood pressure readings, the mean arterial pressure and the heart rate during extubation were significantly higher than those before anaesthesia in both the treatment and the control groups ( $p < 0.05$ ). However, they increased more significantly in the control group than in the treatment group ( $p < 0.05$ ) (Table 2).

### Tube tolerance time, sore throat and pharyngeal discomfort in both groups

The tube tolerance time in the treatment group was significantly longer than that in the control group ( $p < 0.05$ ). The incidence of sore throat and pharyngeal discomfort in the treatment group was significantly lower than that in the control group ( $p < 0.05$ ) (Table 3).

### Level of perceived pain intensity during the procedure

We applied lidocaine-prilocaine cream to the patients in the treatment group 5 minutes ( $n = 6$ ), 10 minutes ( $n = 6$ ), 15 minutes ( $n = 6$ ), 20 minutes ( $n = 6$ ), 25 minutes ( $n = 6$ ) and 30 minutes ( $n = 6$ ) before surgery, respectively. The patients in the treatment and control groups were asked to specify their levels of perceived pain. The results suggested that the application of lidocaine-prilocaine cream 20 minutes before surgery significantly reduced the pain of the treatment group, compared with the control group ( $p < 0.05$ ) (Fig. 1).

Table 2: Comparison of haemodynamic index before anaesthesia and during extubation in both groups

Groups	n	DBP: before	DBP: during	t	p	SBP: before	SBP: during	t	p	MAP: before	MAP: during	t	p	HR (/min): before	HR (/min): during	t	p
Treatment	36	62.43 ± 4.32	68.53 ± 5.64	5.2228	0.0000	101.03 ± 5.54	112.43 ± 3.24	10.8047	0.0000	72.12 ± 4.32	81.23 ± 5.03	8.3575	0.0000	69.45 ± 3.57	87.43 ± 4.54	18.9365	0.0000
Control	36	62.34 ± 4.35	74.43 ± 5.82	10.1212	0.0000	102.04 ± 5.61	123.04 ± 5.32	16.5220	0.0000	73.02 ± 4.35	86.43 ± 5.54	11.5805	0.0000	69.76 ± 3.57	96.32 ± 5.11	25.9176	0.0000
t		0.0893	4.4282			0.7792	10.3610			0.8930	4.2271			0.3735	7.9110		
p		0.9291	0.0000			0.4384	0.0000			0.3748	0.0001			0.7099	0.0000		

DBP: diastolic blood pressure (mmHg); SBP: systolic blood pressure (mmHg); MAP: mean arterial pressure (mmHg); before: before anaesthesia; during: during extubation.

Table 3: Comparison of tube tolerance time, sore throat and pharyngeal discomfort in both groups

Groups	n	Tube tolerance time (min)	Sore throat (n (%))	Pharyngeal discomfort (n (%))
Treatment	36	13.34 ± 2.43	2 (5.41)	3 (8.11)
Control	36	10.03 ± 1.84	8 (21.62)	13 (35.14)
$t/\chi^2$		6.6056	$\chi^2 = 4.1625$	$\chi^2 = 7.9741$
p		0.0000	0.0413	0.0047

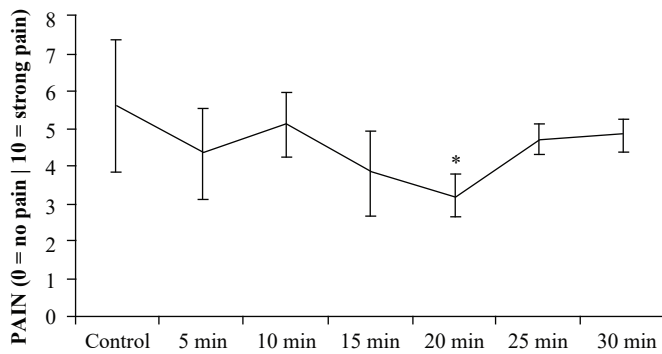


Fig. 1: The level of perceived pain of the patients during the surgery procedure. The time points indicate the application intervals of the cream before surgery. \* $p < 0.05$  presented as statistical significance compared with the control group.

## DISCUSSION

There were three stages during the implementation of general anaesthesia: induction, maintenance and recovery (12). When the patients were in the recovery state after anaesthesia, the extubation process and the suction of sputum tended to stimulate the sympathico-adrenomedullary system (13), and induced the release of catecholamine, which subsequently resulted in the rise of blood pressure and heart rate and consequently increased the risk of cardiovascular events (14). The present study suggested that lidocaine-prilocaine cream decreased the changes in haemodynamics, which indicated that lidocaine-prilocaine cream could reduce the stimulation from the extubation process and from the suction of sputum.

Several studies indicated that lidocaine-prilocaine cream, as one of the local anaesthetics, showed a good skin mucosa permeability, which can hinder the nerve conduction stimulated by the compression and relative displacement between the tracheal mucosa and the trachea catheter (15–17). It was suggested that lidocaine-prilocaine cream relieved the respiratory irritant effect induced by the trachea catheter and increased the endotracheal tube tolerance time. When the patients were subjected to LCRIA, the tube tolerance time was significantly longer than those who had the conventional induction of anaesthesia. The process was mainly performed in non-invasive conditions, which were involved in the inhibition of sympathetic nerve excitation by lidocaine-prilocaine cream. Lidocaine-prilocaine cream combined with the rapid induction of anaesthesia was administered on the tracheal mucosa and can enhance endotracheal tube tolerance time. This might result from the decrease of myocardial oxygen consumption by lidocaine-prilocaine cream in patients with extubation (18).

The degree of comfort can be one of the effective indicators to evaluate the efficacy of the anaesthetic agent. The post-operative follow-up showed that a more effective method to reduce post-operative respiratory adverse reactions was a plenitude of topical anaesthesia. Lidocaine-prilocaine cream performed important roles, such as anti-itching, anti-allergic, anti-inflammatory and analgesic effects (19), which reduced the incidence of pharyngeal mucosa oedema and effectively relieved post-operative sore throat. The study showed that the

application of LCRIA could significantly reduce the incidence of sore throat and throat discomfort compared with the conventional induction of anaesthesia, suggesting that LCRIA could improve the comfort of patients. The possible mechanism may be the lubricating effect of lidocaine-prilocaine cream at the end of the endotracheal tube, thereby reducing the stimulation to the respiratory mucosa induced by the tracheal catheter. Lidocaine-prilocaine cream would block the reaction induced by the pharynx nerve under stimulation, and consequently reduce the response caused by unbearable endotracheal tube in the anaesthesia recovery period (20).

Our results examined the time of lidocaine-prilocaine cream application before surgery. When lidocaine-prilocaine cream was applied < 15 minutes before surgery, the level of pain was high and unstable compared to when it was applied > 15 minutes before surgery. This indicated that lidocaine-prilocaine cream may not be absorbed well if applied less than 15 minutes before surgery.

## CONCLUSION

The application of LCRIA to patients for ovarian cystectomy can effectively alleviate the extubation stress reactions such as haemodynamic fluctuations, enhance endotracheal tube tolerance time and reduce the incidence of sore throat and pharyngeal discomfort.

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