

# Effects of different analgesia regimens on early post-operative cognitive dysfunction in elderly patients undergoing radical resection of cervical carcinoma

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**Abstract.** This study was designed to compare the effects of epidural and intravenous analgesia on early post-operative cognitive dysfunction (POCD) in elderly patients undergoing radical resection of cervical cancer. For this purpose, 74 patients aged 60-78 years [body mass index (BMI), 18-25 kg/m<sup>2</sup>; American Society of Anesthesiologists (ASA) classification score of I-III] undergoing radical resection of cervical cancer were divided into the epidural group (group E) and parenteral group (group P) groups (37 patients in each group). All patients underwent their surgical procedures under epidural anesthesia and intravenously-delivered general anesthesia. Patient-controlled analgesia (PCA) was supplied for 72 h after the surgery. Epidural analgesia was provided for the patients in group E and intravenous analgesia was provided for those in group P. General patient information was recorded and peripheral blood neutrophil counts, C-reactive protein (CRP) levels and interleukin (IL)-6 concentrations were measured immediately prior to the surgery (T<sub>0</sub>), and at 24, 48 and 72 h after the procedure (T<sub>1</sub>, T<sub>2</sub> and T<sub>3</sub>, respectively). Visual analog scale (VAS) scores were also recorded at T<sub>1</sub>, T<sub>2</sub> and T<sub>3</sub>, and the mini-mental state evaluation (MMSE) scores at T<sub>0</sub>, T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> were calculated. Patients were diagnosed as having POCD according to their MMSE score differences between the peri-operative and post-operative values. The results revealed that the levels of CRP and IL-6 significantly increased in both groups after the surgery (T<sub>1-3</sub>). However, the CRP and IL-6 levels in group E were significantly lower than those in group P at all time points examined (P<0.05). The VAS scores in group E at T<sub>1</sub>, T<sub>2</sub> and T<sub>3</sub> were significantly lower than those in group P (P<0.05). Finally, the incidence of POCD in group

E was significantly lower than that in group P (P<0.05). On the whole, the post-operative epidural analgesia reduced the systemic inflammatory response, the perceived pain, and the incidence of POCD in patients undergoing radical resection of cervical cancer, when compared with the effects of intravenous analgesia.

## Introduction

Post-operative cognitive dysfunction (POCD) is a common post-operative complication affecting the central nervous system in elderly patients. It leads to increased medical costs for patients, impairs their recovery after surgery, and can even increase mortality (1). Risk factors for POCD include pain and being of the female sex (2,3), and the incidence of POCD is higher in elderly patients undergoing cardiovascular and orthopedic surgical procedures (4). Unfortunately, studies on POCD incidence and severity in post-menopausal elderly women are limited, with some attention paid to this population cohort in the context of breast cancer treatment (5,6). Thus, the present study was designed to compare the effects of epidural and intravenous analgesia on early POCD in elderly women undergoing the radical resection of cervical cancer.

## Patients and methods

**Patient information.** The Ethics Committee of Huzhou Maternity and Child Health Care Hospital approved this retrospective medical records review (Ethics committee no. 201818), and all patients signed informed consent forms. In total, 74 patients were enrolled [aged 60-78 years; body mass index (BMI), 18-25 kg/m<sup>2</sup>; American Society of Anesthesiologists (ASA) classification score of I-III] from January to December, 2018, who were undergoing radical resection of cervical cancer in our hospital. The pre-operative mini-mental state evaluation (MMSE) scores (7,8) of all the patients were >24. Patients with abnormal coagulation functions, local infection of epidural puncture sites, and severe heart, brain, liver, kidney, or other organ diseases, those with mental illness, central nervous system diseases, and a history of chronic pain, or of allergies, and abuse, or dependence to local anesthetics were excluded. Patient-controlled analgesia (PCA) was supplied for 72 h after

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the surgery. A random number table was used to divide the patients into 2 groups as follows: Those receiving epidural analgesia after the surgery (group E) and those receiving those receiving parenteral analgesia after the surgery (group P), with 37 patients in each group. No statistically significant differences were observed in terms of the general information between the patients in both groups ( $P>0.05$ ; Table I).

**Anesthetic methods.** All patients fasted for 6 h, and were deprived of water beginning 2 h prior to the surgery. After entering the operating room, the patients inhaled oxygen by masks, and their electrocardiogram (ECG), heart rate (HR), blood pressure (BP), blood oxygen saturation (SPO<sub>2</sub>) and bispectral index (BIS) were monitored. Crystalloid infusions were provided at a rate of 6 ml/kg/h and the surgeons completed the procedures under epidural combined with intravenous general anesthesia. For the epidural anesthesia method, patients were asked to adopt a left lateral position, and the anesthesiologist performed an epidural puncture between the L2-3 vertebral bodies and inserted a catheter 3-4 cm to the head side. Subsequently, the anesthesiologist infused 3 ml of 1% lidocaine and checked for local anesthetic poisoning or total spinal anesthesia; in the absence of these phenomena, 10 ml 0.75% ropivacaine were additionally infused. For the intravenous general anesthesia method, the anesthesiologist used midazolam (0.05 mg/kg), sufentanyl (0.5 mg/kg), etomidate (0.3 mg/kg), and cisatracurium (0.15 mg/kg) in sequence for induction. The mechanical ventilation after the tracheal intubation then commenced with a tidal volume of 6-8 ml/kg, a respiratory frequency of 12 times/min, and breath-to-breath ratio of 1:2. Propofol 2-10 mg/kg/h and remifentanyl 0.1-0.3 µg/kg/h were infused intravenously, and cisatracurium was added intermittently during the procedure. The end-tidal CO<sub>2</sub> (PetCO<sub>2</sub>) was maintained at 35-45 mmHg and the bispectral index (BIS) value at 40-60. If the mean arterial pressure of a patient decreased >20% of the pre-operative value, deoxyepinephrine (50-100 µg) was administered intravenously. The anesthesiologist discontinued all anesthetics 10 min prior to the end of the procedure, and ondansetron (8 mg) was administered intravenously. All patients were observed in the recovery room following extubation. PCA analgesia pumps were installed half an hour prior to the end of the surgery and until 72 h thereafter. The patients in group E were connected to an epidural analgesia pump (0.125% ropivacaine; background dose, 8 ml/h; PCA dose, 2 ml/time; at 20-min intervals). The patients in group P were connected to an intravenous analgesia pump (sufentanyl 1.5 µg/kg; background dose, 2 ml/h; PCA dose, 2 ml/time; at 20-min intervals). Diazepam (5 mg) was prescribed for patients in any group with visual analog scale (VAS) scores >4 points (9). Briefly, patients were asked to rate their pain level by placing a single mark along a 10 cm line, with the left end (0 cm) representing 'no pain' and the right end (10 cm) representing 'worst pain'. The distance from the mark to the left end in centimeters was taken as the VAS score.

**Observation index.** The background information was recorded of all the patients. The peripheral blood neutrophil levels, C-reactive protein (CRP) levels and interleukin (IL)-6 concentrations were measured before the surgery (T<sub>0</sub>), and at 24, 48 and 72 h after the surgery (T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub>, respectively) in all

patients. In addition, the T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> VAS scores, and T<sub>0</sub>, T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub> MMSE scores (10) (27-30 points, normal; cognitive impairment, <24 points; POCD, post-operative score 2 points lower than pre-operative score) were calculated.

**Statistical analysis.** All data using SPSS 13.0 statistical software (Leadtools). Measurement data are expressed as the means ± standard deviation (means ± SD), and count data were compared using Chi-squared tests. For comparisons between 2 groups, the independent sample t-test was used. All P-values <0.05 were considered to indicate statistically significant differences.

## Results

In total, 3 patients were found with epidural catheter slip-page in group E, and 1 patient with analgesic pump failure in group P; thus, their data were excluded from the analysis. No significant intraoperative differences were found between the 2 groups ( $P>0.05$ ; Table II).

In addition, the peripheral blood neutrophil counts were similar between the 2 groups at each time point. The levels of CRP and IL-6 increased significantly in both groups after the surgery (T<sub>1-3</sub>). The levels of CRP and IL-6 in group E were significantly lower than those in group P at each time point ( $P<0.05$ ; Table III).

The VAS scores in group E at T<sub>1</sub>, T<sub>2</sub> and T<sub>3</sub> were significantly lower than those in group P at the same time points ( $P<0.05$ ; Table IV). In addition, no significant differences were observed in the pre-operative MMSE scores between the patients in the 2 groups. However, the post-operative MMSE scores at each time point in group E were significantly higher than those in group P ( $P<0.05$ ). The incidence of POCD in group E was significantly lower than that in group P ( $P<0.05$ ; Table V).

## Discussion

POCD is a common postoperative complication and its risk factors include the education level, the presence of hypertension, diabetes mellitus and other comorbidities (11). Age is an independent risk factor for POCD (12), and the incidence of POCD in elderly patients is higher than that in younger patients. Estrogen exerts protective effects on cognitive function (13). The incidence of POCD in menopausal elderly women increases with the gradual estrogen secretion decreases. In our clinical practice, the incidence of POCD is approximately 18.57% in elderly patients undergoing the radical resection of cervical cancer, and this percentage is in agreement with the published incidence of 17 to 43% in elderly patients following non-cardiac surgery (9).

The central cholinergic system plays an important role regulating cognitive function (14). Atropine (an anticholinergic drug) can increase the concentration of acetylcholine, influencing the central cholinergic system (15). In order to avoid the effects of cholinergic blockers on POCD, we avoided using cholinergic drugs throughout the peri-operative period. Phenylephrine increases the cerebral blood flow and oxygen consumption, causing an imbalance in brain metabolism that can lead to POCD (16). In this study, no significant differences

Table I. Comparison of general information between the 2 groups of patients.

Group	Age (years)	BMI (kg/m <sup>2</sup> )	ASA (I/II/III)	Years of education	Diabetes n (%)	Hypertension n (%)
Group E	67.5±2.8	22.3±2.3	5/30/2	6.1±1.0	5 (13.5)	11 (29.7)
Group P	68.4±3.2	22.8±2.6	4/30/3	6.2±1.1	4 (10.8)	13 (35.1)

No significant differences were found between the 2 groups. BMI, body mass index; ASA, American Society of Anesthesiologists (ASA) classification score.

Table II. Comparison of intraoperative conditions between the 2 groups.

Group	Case no.	Operative time (min)	Intraoperative bleeding volume (ml)	Remifentanyl dosage (mg)	Oxygenated adrenaline dosage (μg)	Remedy analgesia rate n (%)
E	34	145.6±13.5	240.8±26.3	1.4±0.2	20.3±7.1	2 (5.9%)
P	36	151.3±14.8	235.9±30.5	1.5±0.4	25.1±8.2	3 (8.3%)

No significant differences were found between the 2 groups.

Table III. Comparison of neutrophil counts, and the levels of CRP and IL-6 between the 2 groups at different time points.

Time point	Group E			Group P		
	Neutrophils (%)	CRP (mg/l)	IL-6 (pg/ml)	Neutrophils (%)	CRP (mg/l)	IL-6 (pg/ml)
T0	69.7±3.9	55.1±8.9	27.1±6.9	70.8±2.5	53.6±8.1	29.7±8.0
T1	70.2±3.3	94.4±7.4 <sup>a</sup>	95.2±6.8 <sup>a</sup>	69.9±2.8	99.6±9.7	102.5±9.1
T2	70.0±3.5	98.3±9.9 <sup>a</sup>	64.3±5.5 <sup>a</sup>	69.2±2.3	111.0±11.2	86.8±6.7
T3	67.1±2.4	66.5±5.7 <sup>a</sup>	32.6±8.9 <sup>a</sup>	67.7±2.1	78.3±8.6	57.2±7.3

<sup>a</sup>P<0.05, compared with group P. CRP, C-reactive protein; IL-6, interleukin 6.

Table IV. Comparison of the mean VAS scores between the 2 groups at different time points.

Group	T1	T2	T3
E	3.1±0.9	3.0±0.7 <sup>a</sup>	2.8±0.5 <sup>a</sup>
P	3.8±1.5	3.5±1.0	3.1±0.6

<sup>a</sup>P<0.05, compared with group P. VAS, visual analog scale.

Table V. Comparison of the MMSE scores and the POCD incidence between the 2 groups at different time points.

Group	T0	T1	T2	T3	POCD incidence
E	28.8±2.0	25.3±2.7 <sup>a</sup>	25.2±2.8 <sup>a</sup>	26.7±2.1 <sup>a</sup>	3 (8.1%) <sup>a</sup>
P	28.5±2.2	23.7±2.9	23.3±2.2	25.5±2.3	10 (27.8%)

<sup>a</sup>P<0.05, compared with group P. MMSE, mini-mental state evaluation; POCD, post-operative cognitive dysfunction.

were found in pre-operative complications, intraoperative medications, or surgical conditions between the 2 groups.

It has been demonstrated that inflammation in the central system is the initiating event in the pathogenesis of POCD (17).

The pathological state of the cancer in patients may promote central nervous system inflammation (18), and the release of inflammatory mediators during the surgery may further affect the function of the central nervous system, leading to POCD. Thus, reducing the post-operative systemic inflammatory response may help to reduce the incidence of POCD. IL-6 and CRP are systemic inflammatory response markers, and IL-6 can also be used as a reliable indicator for assessing the presence of POCD (19). From our observations, the surgeries caused increases in the levels of CRP and IL-6 in all patients; however, the levels of CRP and IL-6 in the patients in group E were significantly lower than those in the patients in group P, suggesting that epidural analgesia is better for controlling inflammation than intravenous analgesia.

Pain is a post-operative risk factor for POCD (2,20). Effective post-operative analgesia does not only relieve pain and improve comfort, but also reduces the release of catecholamines and other stress hormones during the post-operative period (21), and these factors should reduce the incidence of POCD. In this study, the mean post-operative VAS scores of group E were lower than those of group P at each time point, suggesting that epidural analgesia is more effective. Studies have concluded that the VAS score is an independent risk factor for POCD (22), and they have also shown that opioids affect post-operative cognitive function in patients, whether administered intravenously or through the epidural route (23,24). Therefore, in this study, although both the MMSE scores of the E and P groups were significantly lower after surgery (the MMSE score was lowest at 48 h post-surgery), the mean MMSE scores in group E were higher than those in group P at each time point, and the incidence of POCD in the patients in group E was also lower than that of the patients in group P.

In conclusion, the findings of this study suggest that the use of post-operative epidural analgesia can reduce the systemic inflammatory response, as it provides an effective analgesic effect and reduces the incidence of POCD in patients undergoing radical resection of cervical cancer tumors. Therefore, the use of post-operative epidural analgesia is worthy of further investigation and clinical promotion.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Authors' contributions

WY conceived and designed the study; WY and HM carried out experiments; WY and PQ analyzed the data and wrote the manuscript; WY, HM, and PQ reviewed and edited the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The Ethics Committee of Huzhou Maternity and Child Health Care Hospital approved this retrospective medical records review (Ethics committee no. 201818). All of the patients signed patient consents prior to enrollment in the study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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