GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Effects of analgesia methods on serum IL-6 and IL-10 levels after cesarean delivery

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Genet. Mol. Res. 14 (2): 4778-4783 (2015)
Received September 3, 2014
Accepted December 9, 2014
Published May 11, 2015
DOI http://dx.doi.org/10.4238/2015.May.11.10

ABSTRACT. This study aimed to discuss the effects of 3 different analgesia methods on serum IL-6 and IL-10 in patients after cesarean delivery. Thirty full-term women, who underwent cesarean delivery, were randomly assigned to 3 analgesia groups (10 cases each) as follows: intramuscular injection of 100 mg pethidine (NC group), patient controlled epidural analgesia (PCEA) of 5 mg morphine plus 150 mg ropivacaine (MR group), and patient controlled intravenous analgesia (PCIA) of 150 mg sufentanil plus 5 mg droperidol (SF group). An electronic analgesia pump was available in all 3 groups. At 4, 12, 24, and 48 h after surgery, visual analogue scale (VAS) pain scores were evaluated, IL-6 and IL-10 serum levels were measured, and adverse reactions were documented. The MR and SF groups responded well to analgesia. VAS scores at 12 and 24 h in these 2 groups were significantly lower than those in the NC group ($P < 0.05$). IL-6 and IL-10 levels were elevated to varying degrees postoperatively in all 3 groups. In the MR and SF groups, no significant difference occurred at each time point ($P > 0.05$), but compared with the NC group, significant differences were observed at 12 and 24 h ($P < 0.05$). Both PCIA and PCEA produced good analgesic effect, decreased postoperative level of serum IL-6,

promoted release of anti-inflammatory factor IL-10, maintained balance in postoperative serum IL-6 level, and reduced the postoperative inflammatory response. Adverse reactions were significantly higher with epidural morphine than with intravenous sufentanil.

Key words: Analgesia; Interleukin-6; Inflammatory response; Interleukin-10

INTRODUCTION

With cesarean delivery, large incisions and locally intense postoperative pain cause endocrine changes in systemic nerves and production of inflammatory mediators, which in turn, aggravate pain and lengthen its duration. Therefore, immediate and effective anesthesia after cesarean delivery is essential to reduce the stress response and promote postoperative recovery. The most common methods of postoperative analgesia used after cesarean delivery are patient controlled intravenous analgesia (PCIA) and patient controlled epidural analgesia (PCEA), both of which provide good analgesic effect. This study aims to discuss the effects of intramuscular pethidine, PCIA, and PCEA analgesia methods on serum levels of IL-6 and IL-10 in patients undergoing cesarean delivery.

MATERIAL AND METHODS

General material

This study was authorized by the Ethics Committee of No. 1 People's Hospital of Shunde, and an informed consent was signed by all patients. Between April 10 and June 30, 2013, 30 American Society of Anesthesiologists physical status I and II women (ages 21-35 years, weight 55-86 kg, and height 151-175 cm), underwent cesarean delivery and were not treated with other analgesic drugs before and after surgery.

Anesthesia and analgesia

After patients arrived in the operating room, venous access was established and vital signs were regularly monitored. Intervertebral space puncture of L2-3 or L3-4 was performed in association with combined spinal-epidural anesthesia. After successful puncture, 2 mL 0.5% bupivacaine was infused for lumbar anesthesia, and a 4-cm epidural catheter was placed in the epidural space. When intraoperative systolic pressure declined by 30% above baseline, IV bolus of ephedrine, and when the heart rate falls below 50 bpm, IV bolus administration of atropine caused the heart rate to increase above 50 bpm. Ten minutes before the end of surgery, 0.3 mg ramosetron was given by intravenous injection. Patients were assigned postoperatively to one of 3 analgesia groups: intramuscular injection of 100 mg pethidine (NC group), PCEA administration of 5 mg morphine plus 150 mg ropivacaine (MR group), or PCIA administration of 1.5 μg/mL sufentanil plus 5 mg droperidol (SF group). An electronic analgesia pump with a total volume of 100 mL was used (2 mL/h continuous dose, 1 mL/self-controlled dose, 15 min lock time, and 8 mL/h controlled maximum dose).

Collection and management of samples

Venous blood (3 mL) was collected in an anticoagulation tube preoperatively and postoperatively at 4, 12, 24, and 48 h. After centrifugation, the supernatant was stored in a refrigerator at -80°C. Then, IL-6 and IL-10 serum levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA).

Observation indicators

Visual analogue scale (VAS) pain score was recorded postoperatively at 4, 12, 24, and 48 h, and peripheral venous blood was obtained for ELISA measurement of IL-6 and IL-10 serum levels. Criteria for VAS scores were as follows: painless = 0, and unbearable pain = 10. Analgesic effects were considered good (<3), satisfactory (3-5), or poor (>5).

Patients were observed for the presence of adverse reactions such as nausea and vomiting, urinary retention, pruritus, and drowsiness. Postoperative accumulative analgesic doses and patient controlled analgesia pressing times were recorded. Patients were questioned regarding their level of satisfaction with postoperative analgesics.

Statistical treatment

Measurement data are reported as weighted mean difference using the SPSS 17.0 statistical software (Chicago, IL, USA). Independent sample *t*-test was used for comparison between 2 groups. One-way analysis of variance was used at different time points in a group. The χ^2 test was used for enumeration data and was tested with significant difference ($P < 0.05$).

RESULTS

No significant differences were observed in age, height, weight, or surgery duration among 3 groups of patient*s* ($P > 0.05$), as shown in Table 1.

Table 1. Comparison of general data in 3 groups of patients (means ± SD, N = 10).

Groups	Age	Length (cm)	Height (kg)	Surgery duration (min)
NC group	28.1 ± 3.8	157.7 ± 4.1	70.3 ± 6.3	42.6 ± 4.2
MR group	27.3 ± 3.0	159.8 ± 4.0	68.8 ± 5.9	43.5 ± 4.7
SF group	26.5 ± 3.0	162.7 ± 5.2	71.9 ± 6.1	41.7 ± 4.1

NC = intramuscular injection of 100 mg pethidine; MR = patient controlled epidural analgesia of 5 mg morphine plus 150 mg ropivacaine; SF = patient controlled intravenous analgesia of 150 mg sufentanil plus 5 mg droperidol.

VAS scores in 3 groups indicated better analgesic effects at each time point compared with the MR group and SF group. No significant differences were observed in VAS scores at each time point between 2 groups ($P > 0.05$). VAS score was significantly lower in 2 groups than in the NC group at 12, 24, and 48 h, ($P < 0.05$), as shown in Table 2.

Comparison of IL-6 and IL-10 serum levels in 3 groups of patients

Postoperative IL-6 and IL-10 serum levels were elevated to varying degrees in 3

groups. No significant differences were seen at each time point in the MR and SF groups ($P > 0.05$). IL-6 and IL-10 levels at 12 and 24 h in the MR and SF groups were significantly lower than those in the NC group ($P < 0.05$), as shown in Table 3.

Table 2. Comparison of VAS scores at different time points in 3 groups of patients (means ± SD).

Groups	Postoperative 4 h	Postoperative 12 h	Postoperative 24 h	Postoperative 48 h
NC group	2.1 ± 0.6	7.3 ± 1.1$^{\Delta}$	5.1 ± 1.2$^{\Delta}$	2.6 ± 0.4
MR group	2.3 ± 0.7	3.0 ± 0.7$^{\blacktriangle}$	2.7 ± 0.9$^{\blacktriangle}$	1.6 ± 0.4$^{\blacktriangle}$
SF group	2.3 ± 0.6	2.6 ± 0.7$^{\blacktriangle}$	2.9 ± 0.4$^{\blacktriangle}$	1.5 ± 0.3$^{\blacktriangle}$

Compared with score at the same time point in the NC group, $^{\blacktriangle}P < 0.05$; compared with score at 4 h, $^{\Delta}P < 0.05$. VAS = visual analogue scale; NC = intramuscular injection of 100 mg pethidine; MR = patient controlled epidural analgesia of 5 mg morphine plus 150 mg ropivacaine; SF = patient controlled intravenous analgesia of 150 mg sufentanil plus 5 mg droperidol.

Table 3. Changes in IL-6 and IL-10 levels at different time points in 3 groups (pg/mL, means ± SD).

Indicators	Groups	Pre-operative	Post-operative 4 h	Post-operative 12 h	Post-operative 24 h	Post-operative 48 h
IL-6	NC groups	5.28 ± 0.95	28.83 ± 3.49$^{\blacktriangle}$	56.59 ± 4.02$^{\blacktriangle}$	44.12 ± 3.81$^{\blacktriangle}$	18.92 ± 2.96$^{\blacktriangle}$
	MR groups	5.65 ± 0.89	24.84 ± 3.14$^{\blacktriangle}$	33.28 ± 5.17$^{\blacktriangle\Delta}$	29.51 ± 5.79$^{\blacktriangle\Delta}$	12.71 ± 4.66$^{\blacktriangle}$
	SF groups	5.68 ± 1.02	22.81 ± 5.95$^{\blacktriangle}$	33.63 ± 5.72$^{\blacktriangle\Delta}$	30.91 ± 7.42$^{\blacktriangle\Delta}$	13.05 ± 4.13$^{\blacktriangle}$
IL-10	NC groups	36.03 ± 7.56	49.31 ± 8.53$^{\blacktriangle}$	107.28 ± 8.59$^{\blacktriangle}$	92.26 ± 6.85$^{\blacktriangle}$	40.62 ± 6.40
	MR groups	31.51 ± 6.83	50.01 ± 8.89$^{\blacktriangle}$	81.08 ± 8.51$^{\blacktriangle\Delta}$	80.30 ± 6.02$^{\blacktriangle\Delta}$	33.07 ± 6.17
	SF groups	30.62 ± 6.11	46.83 ± 8.64$^{\blacktriangle}$	78.17 ± 7.99$^{\blacktriangle\Delta}$	79.70 ± 5.66$^{\blacktriangle\Delta}$	34.63 ± 6.09

Compared with preoperative level, $^{\blacktriangle}P < 0.05$; compared with level at the same time point in the NC group, $^{\Delta}P < 0.05$. IL = interleukin; NC = intramuscular injection of 100 mg pethidine; MR = patient controlled epidural analgesia of 5 mg morphine plus 150 mg ropivacaine; SF = patient controlled intravenous analgesia of 150 mg sufentanil plus 5 mg droperidol.

Comparison of adverse reactions in 3 groups of patients

Incidences of adverse reactions in 10 cases were significantly higher in the MR group, and the incidence of pruritus was significantly higher in the MR group than in the other 2 groups ($P < 0.05$). Incidences of drowsiness in the MR and SF groups were significantly lower than the incidence of drowsiness in the NC group ($P < 0.05$), as shown in Table 4.

Table 4. Adverse reactions in 3 groups during postoperative analgesia period N (%).

Groups	Cases	Adverse reactions			
		Urinary retention	Nausea and vomiting	Pruritus	Drowsiness
NC group	10	0 (0%)	1 (10%)	0 (0%)	4 (40%)
MR group	10	1 (10%)	2 (20%)	3 (20%)$^{\blacktriangle}$	0 (0%)$^{\blacktriangle}$
SF group	10	0 (0%)	1 (10%)	0 (0%)	0 (0%)$^{\blacktriangle}$

Compared with occurrences in the NC group, $^{\blacktriangle}P < 0.05$. NC, intramuscular injection of 100 mg pethidine; MR, patient controlled epidural analgesia of 5 mg morphine plus 150 mg ropivacaine; SF, patient controlled intravenous analgesia of 150 mg sufentanil plus 5 mg droperidol.

DISCUSSION

This study showed that postoperative pain can cause release of large amounts of cell inflammatory factors, including those from wound tissue, into the blood. Good postoperative analgesia can inhibit migration of cytokines, slowing down movement of pro-inflammatory factors to wound tissue and reducing release of inflammatory factors. Wounds can recover quickly in this context (Schmidt et al., 1997; Lahav et al., 2002; Carvalho et al., 2013). Therefore, immediate and effective postoperative analgesia can not only relieve delivery-induced pain, but can also inhibit the body's stress response to varying degrees and reduce release of inflammatory mediators, improving the postoperative inflammatory response.

As one of the main pro-inflammatory cytokines, IL-6 is a marker of surgical tissue damage and to some degree, can be a measure of the severity of the operative wound. Its elevation is an especially sensitive indicator of an early wound. Therefore, inhibition of the release of IL-6 is beneficial for the body to recover postoperatively. IL-6 is also an important mediator of postoperative pain; it increases amounts of inflammatory cytokines in the central nervous system through activation of glial cells after peripheral nerve injury, causing a nerve inflammatory reaction and central pain (Torres et al., 2007). Our study found that the IL-6 level in 3 groups of patients who underwent cesarean delivery began to rise postoperatively at 4 h, peaked at 12 and 24 h, and then gradually declined. The IL-6 level in the NC group rose more substantially than that in the other 2 groups ($P < 0.05$), indicating that elevation of the IL-6 level was caused by pain. This signifies that effective postoperative analgesia can inhibit the inflammatory reaction from pain in women after cesarean delivery and can significantly reduce the IL-6 level.

The emergence of IL-10, an important anti-inflammatory cytokine, by activation of immune cells (peripheral blood T cells, mononuclear cells, and mast cells) and non-immune cells (keratinocytes and epithelial cells) within the body, is characterized by strong anti-inflammatory activity (Mosser and Zhang, 2008). Overexpression of IL-10 can markedly reduce the inflammatory reaction from skin damage (Peranteau et al., 2008) and can downregulate IL-6 and other pro-inflammatory factor levels (Sun et al., 2010). Some studies have showed that plasma IL-10 levels increase after major surgery (Weis et al., 2009; Simsek et al., 2013). These studies also showed that IL-6 and IL-10 are critical in tissue damage and wound healing, respectively. The present study found that changes in serum IL-10 levels were similar to those in IL-6 levels in 3 groups of patients after cesarean delivery; levels started to rise postoperatively at 4 h, peaked at 12 and 24 h, and then gradually declined. At 48 h postoperatively, the IL-6 level remained higher than it was preoperatively, while the IL-10 level was relatively unchanged. Therefore, two different effects of cytokines emerged-stimulation from the operation and the surgical wound, and an increase in IL-10 level along with elevation of the IL-6 level, maintaining a balance between IL-10 and IL-6 levels.

Comparison of VAS scores in 3 different analgesia groups at different time points showed that continuous intravenous analgesia had comparable effects to epidural analgesia, with VAS scores significantly lower than those in the NC group ($P < 0.05$). However, adverse reactions from morphine epidural analgesia were more severe than those from continuous intravenous analgesia, and the incidence of drowsiness in the NC group was significantly higher. Also, although intramuscular injection of 100 mg pethidine, as needed, postoperatively had some analgesic effect, it caused more frequent adverse reactions.

In summary, in patients who underwent cesarean delivery, PCIA and PCEA produced

good analgesic effect, reduced postoperative IL-6 serum levels, increased release of anti-inflammatory factor L-10, maintained an effective balance in postoperative inflammatory factors, and relieved postoperative inflammatory reaction. However, adverse reactions were significantly higher with epidural morphine than with intravenous sufentanil analgesia.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Research supported by the Science and Technology Bureau of Foshan, Guangdong Province, china (#200908156).

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