

Bilateral Sanyinjiao acupuncture reduces the dose of intravenous remifentanil in labor analgesia

T.T. Wang¹, C. Liang², F.L. Kong¹, B. Dong¹, C. Feng^{1,*}

¹ Department of Anesthesiology, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan (P.R. China)

² Department of General Surgery, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan (P.R. China)

Summary

This study aims to evaluate the effects of intravenous analgesia using remifentanil combined with *Sanyinjiao* acupuncture in child-birth. A total of 150 women who delivered their babies naturally were selected. Among these, 100 women willing to undergo labor analgesia and were full-term and with single child, cephalic presentation, and without pregnancy complications were randomly divided into an intravenous injection group (IV) and a combined injection group (CI), while the remainder comprised the control group (C). After the patients entered the active phase of labor, remifentanil was intravenously infused. Patients in group CI were injected with 2 ml of 1% lidocaine into the bilateral *Sanyinjiao* acupoint. After analgesia began, pain score, mean arterial pressure, and heart rate in group IV and group CI were significantly lower than in group C ($p < 0.05$). The dose of remifentanil was significantly lower in group CI than in group IV ($p < 0.05$); however, there was no significant difference in the duration of labor and neonatal score among the three groups ($p > 0.05$). Neither excessive sedation nor respiratory depression occurred. *Sanyinjiao* acupoint injection combined with intravenous infusion of remifentanil reduced the amount of opioids and the risk for serious adverse reactions.

Key words: Acupoint injection; Sanyinjiao; Remifentanil; Labor analgesia.

Introduction

Pain relief during labor has become a topic of major interest in China, a country with a large childbearing-age population and a new policy for birth control since 2016. Epidural analgesia (EA) is recommended as the first choice for labor analgesia [1]. However, its uptake by pregnant women is restricted in those with spinal abnormalities, bleeding diathesis, suspected infection, or known allergy to local anesthetics or those who refuse to undergo invasive procedures [1]. Therefore, a suitable alternative to EA may be required.

As a selective opioid μ -receptor agonist with a rapid onset of action, remifentanil can rapidly cross the placenta after administration. It is quickly metabolized and redistributed by the fetus by non-specific esterases, thus enabling rapid offset after discontinuation of infusion [2]. For these reasons, remifentanil has been proposed as an ideal systemic analgesic for relief of labor pain. The primary concerns for using intravenous opioids include possible maternal sedation and respiratory changes [3, 4].

Acupuncture and related techniques have been used for > 2,500 years in China and are increasingly practised to alleviate pain and reduce perioperative analgesic consumption in the past decade or two [5-7]. The practice of acupuncture involves using needles at specific points along meridians in the body to regulate energy flow (qi). Non-invasive techniques include acupressure, transcuta-

neous electrical stimulation, and laser stimulation [8]. The mechanism of its effectiveness is based on the theory that acupuncture actually evokes changes via afferent nerves or A-delta fibers in muscles and midbrain structures and via the systemic release of beta-endorphin in addition to adrenocorticotrophic hormone [5, 6, 8]. The SP6 (*Sanyinjiao*) acupoint is located at a width of four fingers or 3 inches immediately above the medial malleolus on the posterior tibial border. A study by Lee *et al.* reported that acupressure at *Sanyinjiao* for 30 minutes effectively decreased labor pain for up to 60 minutes; however, no difference was found with the use of analgesia [9]. Other researchers have suggested that SP6 acupressure appeared to be effective when delivered by trained personnel for some dysmenorrhea symptoms [10].

The goal of the present study was to investigate whether acupuncture at SP6 can reduce remifentanil consumption during labor analgesia [4], and result in fewer undesirable adverse events.

Materials and Methods

A total of 100 patients who intended to undergo painless labor in the authors' hospital between September 2015 and March 2016 were randomly divided into two groups: CI (n = 50) and IV (n = 50). Patients 18-35 years of age, with American Society of Anesthesiologists class I-II, pregnancy ≥ 37 weeks, singleton, cephalic pre-sentation in the active period of labor, and uterine orifice ≤ 5 cm were included. Patients with pregnancy complications, fetal ab-

Table 1. — Comparison of general conditions among the three groups (n=50, $\bar{x}\pm s$)

	Age (years)	Body weight (kg)	Height (cm)	BMI	Gestational week (weeks)
IV(n=50)	28.6 ± 4.1	69.8 ± 8.6	159.5 ± 7.2	27.6 ± 3.3	39.2 ± 1.8
CI(n=50)	27.9 ± 3.8	72.3 ± 8.2	160.9 ± 9.1	28.2 ± 4.5	38.9 ± 1.9
C(n=50)	28.1 ± 3.5	70.2 ± 9.8	161.3 ± 8.2	27.1 ± 3.7	40.5 ± 1.5

Table 2. — Comparison of vital signs among the three groups (n=50, $\bar{x}\pm s$)

Item	Group	Before analgesia	After analgesia						
			5 min	10 min	20 min	30 min	1 h	2 h	End of observation
MAP (mmHg)	IV	86.0±15.0▲	80.0 ± 13.0▲#	79.0 ± 14.0▲#	78.0±13.0▲#	79.0±15.0▲#	76.0±11.0▲#	74.0±14.0▲#	73.0±12.0▲#
	CI	88.0±11.0	79.0 ± 14.0▲#	78.0 ± 12.0▲#	76.0±15.0▲#	78.0±13.0▲#	75.0±12.0▲#	76.0±13.0▲#	72.0±11.0▲#
	C	85.0±17.0	88.0 ± 15.0	86.0±15.0	88.0±14.0	87.0±16.0	79.0±11.0▲#	81.0±13.0▲#	78.0±15.0▲#
HR (Beat/min)	IV	88.0±10.0	81.0±12.0▲#	79.0±13.0▲#	78.0±11.0▲#	78.0±10.0▲#	83.0±15.0▲#	79.0±11.0▲#	76.0±14.0▲#
	CI	86.0±13.0	80.0±11.0▲#	78.0±12.0▲#	77.0±12.0▲#	76.0±13.0▲#	79.0±12.0▲#	77.0±14.0▲#	80.0±13.0▲#
	C	89.0±11.0	88.0±13.0	90.0±10.0	89.0±12.0	90.0±10.0	93.0±17.0	91.0±15.0	96.0±18.0
SpO ₂ (%)	IV	98.5±1.1	98.0±0.9	98.5±1.2	98.3±1.4	98.6±1.1	97.6±1.2	98.3±1.5	96.8±1.0
	CI	98.0±1.0	97.5±1.4	97.8±1.0	98.0±0.9	98.1±1.0	98.0±1.1	97.6±0.7	98.2±1.0
	C	98.9±0.9	98.7±1.0	99.0±0.9	98.8±0.9	98.6±1.1	97.3±1.5	97.6±1.0	97.1±1.3
VAS score	IV	8.2±0.9	4.2±1.3▲#	3.8±1.1▲#	3.3±0.8▲#	2.8±0.7▲#	3.1±0.5▲#	2.5±0.8▲#	2.6±0.4▲#
	CI	8.3±0.7	4.5±1.1▲#	3.4±0.7▲#	3.2±0.6▲#	2.7±0.6▲#	2.5±0.3▲#	2.8±0.2▲#	2.2±0.5▲#
	C	7.8±1.1	8.0±0.9	8.2±1.1	8.6±0.9	8.8±0.7	8.6±0.8▲#	8.8±0.3▲#	9.1±0.4▲#

▲p < 0.05 compared with the value before analgesia; #p < 0.05 compared with group C.

normalities, allergies to opioids or local anesthetics, or mental disorders or those converted to cesarean section for any reason were excluded. Fifty full-term women who had no intention of painless labor were recruited as group C. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science & Technology. Written informed consent was obtained from all participants.

After each patient entered the delivery room, peripheral venous access was established as per routine protocol, and 500 mL of lactated Ringer's solution was intravenously administered, together with nasal cannula for oxygen (oxygen flow rate, 2-4 L/min).

After the labor process entered the active period, patients in group IV and group CI were administered intravenous analgesia using remifentanyl and one self-controlled analgesia instrument (automatic injection pump). The background infusion dose was 4 µg/kg/h, with a single dose (bolus) of 0.2 µg/kg; the lockout time was 2 minutes [9]. Patients in group CI were also injected with 2.5 mL of 1% of lidocaine into the bilateral acupoints of *Sanyinjiao*, respectively, using a No. 7 needle and 5 mL disposable syringe after routine disinfection of the local skin. After injection, the needle was withdrawn and a bandage was applied to the wound. After the uterine orifice was completely open, remifentanyl infusion was discontinued. Mean arterial pressure (MAP), heart rate (HR), and pulse oxygen saturation (SpO₂) were recorded every five minutes before and after the onset of labor analgesia. The visual analog scale (VAS) score was recorded before and at 5, 10, 10, 20, and 30 min at 1 h, and 2 h after the onset of analgesia and at the time of full opening of the uterine orifice.

The Ramsay sedation score [11] was recorded before and at 5, 10, 10, 20, and 30 minutes after the onset of analgesia and at the time of full opening of the uterine orifice. The Ramsay sedation was scored as follows: anxiety, excitement, or restlessness = 1 point, cooperation, obedience, and quiet = 2 points, falling asleep and only responding to commands = 3 points, falling

asleep and responding to mild shaking or loud sound = 4 points, sleeping and responding to noxious stimulation response = 5 points, and sleeping and not responding to the above stimuli = 6 points. Accordingly, 1 point was defined as insufficiently sedated, 2-4 points were defined as satisfactory sedation, and 5-6 points were defined as over-sedation.

Anesthesiologists who were blinded to the patient group allocation participated in maternal monitoring throughout the entire process. If SpO₂ was < 94% and > 40 s or < 90%, verbal stimulation was applied. If the patient did not respond, the patient's shoulder or arm was gently shaken, and the patient was asked to take a deep breath.

The first stage of active labor refers to the period of uterus opening, from 3 cm to fully open, during which period the total amount of remifentanyl infusion was recorded. The second stage of labor refers to the period from full opening of the uterus to delivery of the fetus. The fetal heart rate during labor and Apgar score of the newborn 1 and 5 minutes after delivery were continuously recorded.

Statistical analysis was performed using SPSS version 22.0. The measurement data are expressed as mean ± standard deviation. One-way ANOVA and Dunnett' test were used for comparisons among the three groups, the *t*-test was used for comparison between two groups, and the chi-squared test was used for the comparison of count data; *p* < 0.05 was considered to be statistically significant.

Results

There were no significant differences in age, height, body weight, or gestational weeks among the three groups (*p* > 0.05) (Table 1). Comparison of MAP, HR, and VAS scores among the three groups demonstrated no statistically significant differences before the onset of analgesia (*p* > 0.05).

At 5, 10, 20, and 30 minutes, one and two hours after the onset of analgesia, and at the end of the first stage of labor, the values decreased to levels lower than those before, with statistically significant differences ($p = 0.001$). The values in group IV and group CI were statistically lower than those in group C at all time points ($p = 0.007$). There was no significant change in SpO₂ in each group at any of the time points, with no statistically significant difference among the three groups ($p > 0.05$) (Table 2).

The first active periods of labor in groups IV, CI, and C were 208.8 ± 45.1 , 203.7 ± 47.5 , and 198.5 ± 56.1 minutes, respectively. The second active periods of labor in groups IV, CI, and C were 54.5 ± 15.8 , 58.7 ± 21.1 , and 55.6 ± 24.8 minutes, respectively, with no statistically significant difference among the three groups ($p > 0.05$).

The mean total doses of maternal intravenous remifentanyl in group IV and group CI were 1283.1 ± 215.7 μg and 1157.3 ± 145.7 μg , respectively; the difference was statistically significant ($p = 0.010$). Common adverse reactions included sedation and lethargy; however, all patients were awakened by verbal stimulation. The Ramsay sedation score was < 4 points in all patients, and no cases of excessive sedation occurred. Some patients in each group experienced vomiting (group IV [$n = 4$], group CI [$n = 1$], and group C [$n = 2$]).

The Apgar scores in groups IV, CI, and C were 8.1 ± 0.4 , 8.7 ± 0.2 , and 8.2 ± 0.3 , respectively, with five-minute Apgar scores of 9.8 ± 0.2 , 9.8 ± 0.3 , and 9.8 ± 0.2 , respectively. There was no significant difference among the three groups ($p > 0.05$).

Discussion

Clinically, spinal anesthesia is effective for painless delivery, but several complications are possible, including nerve damage and local anesthetic poisoning, and there may exist the risk of puncture failure. In addition, patients with contraindications to spinal puncture, such as puncture infection, thrombocytopenia, spinal deformity or spinal surgery, are not suitable for this method. Although the concentration of local anesthetic in EA is low, the volume is large, and the duration of action is long, which can reduce patients' duration of contractions and prolong labor. Furthermore, some patients may experience motor nerve block after drug withdrawal and increase for device-assisted labor [1]. In addition, studies have found that EA has a higher rate of fever than intravenous analgesia using remifentanyl, which may be related to the effects of EA on temperature regulation [11].

As an ultra-short-acting new opioid, remifentanyl has an onset time of only 30 seconds and a small distribution volume. It is hydrolyzed by non-specific cholinesterase, and the plasma half-life is three to five minutes. Moreover, it washes out rapidly after withdrawal; therefore, long-term use will not result in accumulation. Although it can pass

through the placental barrier, the apparent distribution volume in neonates is large, and the clearance rate is faster and, therefore, has no effect on neonatal Apgar score [3]. Therefore, remifentanyl is more effective for clinical venous labor analgesia than conventional meperidine, and has no limit in the timing of administration [12-14], but its analgesic efficiency may not be as high as EA [15, 16].

Results of this study suggest that intravenous remifentanyl for labor analgesia can reduce pain in the active period, while it does not prolong the labor process or affect the neonatal Apgar score, consistent with a study by Volmanen *et al.* [17]. The reason may be that opioids can increase the threshold of body pain and produce a degree of sedation and euphoria, thus enabling mothers to tolerate more severe pain [17].

Studies have shown that the average dose of intravenous of remifentanyl for effective analgesia is 0.06 $\mu\text{g}/\text{kg}/\text{min}$ utes, and the average self-controlled bolus dose is 0.4 $\mu\text{g}/\text{kg}$. No significant changes in fetal heart rate can be caused within such doses; however, when the dose is increased to 0.08 $\mu\text{g}/\text{kg}/\text{min}$ ute, maternal SPO₂ may decrease, and doses increased to 0.1 $\mu\text{g}/\text{kg}/\text{min}$ may decrease fetal heart rate [10]. Some investigators have focused on pharmacokinetic studies of remifentanyl, seeking safer and more effective doses and dosing regimens [18] because intravenous opioids carry the risk for maternal respiratory depression and excessive sedation [16, 19]. During the present study, there were no cases of excessive sedation (i.e., Ramsay scores all < 4), and patients who experienced transient percutaneous SPO₂ decrease in group IV and group CI were able to breathe spontaneously and relieve symptoms under anesthesiologists' verbal stimulation. Therefore, no serious adverse reactions, such as respiratory depression, occurred. However, the entire process still needs to be performed under the close supervision of experienced anesthesiologists.

In recent years, applications of traditional Chinese medicine acupuncture and related technologies in the peri-experimental period have received increasing attention in the medical field in China and abroad, especially its application for pain treatment, which has been approved by the World Health Organization [5, 20]. The *Sanyinjiao* acupoint is one of the most commonly used acupoints in uterine-related diseases. It plays a role in the three aspects of connecting the viscera, meridian and acupoints, and achieves analgesic effects through the multiple systems and layers of the neuro-endocrine-immune network [4]. Therefore, it can be safely and effectively used for labor analgesia [21, 22].

This study used *Sanyinjiao* acupuncture for local anesthesia, and the dual effects of combining acupuncture with drugs can, on one hand, block the afference of local pain nerves and, on the other, stimulate the central nervous system to produce endorphins and other analgesic substances, thus working synergistically with intravenous opioids to

achieve good analgesic effects. The results demonstrated that *Sanyinjiao* acupuncture, as a supplement to intravenous labor analgesia, can further reduce the total dose of intravenous use of remifentanyl, which may reduce the occurrence of serious adverse reactions such as potential respiratory depression.

In summary, intravenous remifentanyl combined with *Sanyinjiao* acupuncture can effectively reduce maternal labor pain while neither extending the labor process, increasing the incidence of adverse reactions, nor affecting the neonatal score. Meanwhile, it can reduce the amount of intravenous use of remifentanyl, which further reduces the occurrence of serious adverse reactions. Therefore, it is a safe and effective method for labor analgesia.

Acknowledgments

This paper was supported by Health and Family Planning Commission of Wuhan Municipality, PRC (WX12C49).

Conflict of Interest

The authors declare no competing interests.

Submitted: April 11, 2019

Accepted: June 17, 2019

Published: June 15, 2020

References

- [1] Ranasinghe J.S., Birnbach D.J.: "Progress in analgesia for labor: focus on neuraxial blocks". *Int. J. Womens Health*, 2010, 1, 31.
- [2] Egan T.D.: "Pharmacokinetics and pharmacodynamics of remifentanyl: an update in the year 2000". *Curr. Opin. Anaesthesiol.*, 2000, 13, 449.
- [3] Kan R.E., Hughes S.C., Rosen M.A., Kessin C., Preston P.G., Lobo E.P.: "Intravenous remifentanyl: placental transfer, maternal and neonatal effects". *Anesthesiology*, 1998, 88, 1467.
- [4] Volmanen P., Akural E.I., Raudaskoski T., Alahuhta S.: "Remifentanyl in Obstetric Analgesia: A Dose-Finding Study". *Anesth. Analg.*, 2002, 94, 913.
- [5] Chernyak G.V., Sessler D.I.: "Perioperative acupuncture and related techniques". *Anesthesiology*, 2005, 102, 1031.
- [6] Wang H., Xie Y., Zhang Q., Xu N., Zhong H., Dong H., et al.: "Transcutaneous electric acupoint stimulation reduces intra-operative remifentanyl consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: a prospective, randomized, placebo-controlled trial". *Br. J. Anaesth.*, 2014, 112, 1075.
- [7] Fan A.Y., Miller D.W., Bolash B., Bauer M., McDonald J., Faggert S., et al.: "Acupuncture's Role in Solving the Opioid Epidemic: Evidence, Cost-Effectiveness, and Care Availability for Acupuncture as a Primary, Non-Pharmacologic Method for Pain Relief and Management-White Paper 2017". *J. Integr. Med.*, 2017, 15, 411.
- [8] Pomeranz B., Stux G.: "Scientific Bases of Acupuncture. Springer Verlag"; Berlin, 1989, 1.
- [9] Lee M.K., Chang S.B., Kang D.H.: "Effects of SP6 acupressure on labor pain and length of delivery time in women during labor". *J. Altern. Complement. Med.*, 2004, 10, 959.
- [10] Abaraogu U.O., Igwe S.E., Tabansi-Ochiogu C.S.: "Effectiveness of SP6 (*Sanyinjiao*) acupressure for relief of primary dysmenorrhea symptoms: A systematic review with meta- and sensitivity analyses". *Complement. Ther. Clin. Pract.*, 2016, 25, 92.
- [11] Douma M.R., Stienstra R., Middeldorp J.M., Arbous M.S., Dahan A.: "Differences in maternal temperature during labour with remifentanyl patient-controlled analgesia or epidural analgesia: a randomised controlled trial". *Int. J. Obstet. Anesth.*, 2015, 24, 313.
- [12] Wilson M.J.A., MacArthur C., Hewitt C.A., Handley K., Gao F., Beeson L., et al.: "Intravenous remifentanyl patient-controlled analgesia versus intramuscular pethidine for pain relief in labor (RESPITE): an open-label, multicentre, randomised controlled trial". *Lancet*, 2018, 392, 662.
- [13] Leong W.L., Sng B.L., Sia A.T.: "A comparison between remifentanyl and meperidine for labor analgesia: a systematic review". *Anesth. Analg.*, 2011, 113, 818.
- [14] Wang Z.H., Yang Y., Xu G.P.: "Remifentanyl analgesia during external cephalic version for breech presentation in nulliparous women at term: A randomized controlled trial". *Medicine (Baltimore)*, 2017, 96, e6256.
- [15] Douma M.R., Middeldorp J.M., Verwey R.A., Dahan A., Stienstra R.: "A randomised comparison of intravenous remifentanyl patient-controlled analgesia with epidural ropivacaine/sufentanyl during labor". *Int. J. Obstet. Anesth.*, 2011, 20, 118.
- [16] Stocki D., Matot I., Einav S., Eventov-Friedman S., Ginosar Y., Weiniger C.F.: "A randomized controlled trial of the efficacy and respiratory effects of patient-controlled intravenous remifentanyl analgesia and patient-controlled epidural analgesia in laboring women". *Anesth. Analg.*, 2014, 118, 589.
- [17] Volmanen P., Sarvela J., Akural E.I., Raudaskoski T., Korttila K., Alahuhta S.: "Epidural levobupivacaine with fentanyl for pain relief in early labor: a randomized, controlled, double-blinded study". *Acta Anaesthesiol. Scand.*, 2008, 52, 219.
- [18] Jost A., Blagus R., Ban B., Kamenik M.: "Effect-site concentration of remifentanyl during patient-controlled analgesia in labour". *Int. J. Obstet. Anesth.*, 2015, 24, 230.
- [19] Freeman L.M., Bloemenkamp K.W., Franssen M.T., Papatsonis D.N., Hajenius P.J., Hollmann M.W., et al.: "Patient controlled analgesia with remifentanyl versus epidural analgesia in labor: randomised multicentre equivalence trial". *BMJ*, 2015, 350, h846.
- [20] National Institute of Health: Office of the Director, November, 1997, 3, 3.
- [21] Dong C., Hu L., Liang F., Zhang S.: "Effects of electro-acupuncture on labor pain management". *Arch. Gynecol. Obstet.*, 2015, 291, 531.
- [22] Jiang Q.Y., Wang M.Y., Li L., Mo H.X., Song J.L., Tang Q.L., et al.: "Electroacupuncture relieves labour pain and influences the spinal dynorphin/k-opioid receptor system in rats". *Acupunct. Med.*, 2016, 34, 223.

Corresponding Author:

CHUN FENG, M.D.

Department of Anesthesiology Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology

Wuhan 430016 (P.R. China)

e-mail: docchunfeng@126.com