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Evaluation efficacy and safety of epidural analgesia in second-trimester induced labor

A single-center, prospective, non-randomized, controlled study

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Abstract

Background: Second-trimester induced labor in pregnant women was often more likely to suffer from psychological and physiological double pain. However, the analgesic management received less attention, and the optimal analgesic mode for second-trimester induced labor had not been determined. Our objective was to evaluate the feasible of epidural analgesia (EA) in second-trimester induced labor.

Methods: From January 2020 to December 2021, Primipara who planned to undergo second-trimester induced labor in the First Affiliated Hospital of Yangtze University were collected. The method of labor induction was oral mifepristone + amniotic cavity injection of Ethacridine Lactate. Based on whether or not patients received epidural analgesia, which were divided into EA group (30 cases) and non-EA (NEA) group (30 cases). The primary outcome were visual analog scale (VAS) score of pain and result of follow-up, the secondary outcomes included relative clinical parameter and labor duration.

Results: Vaginal induction of labor was successful in both groups. There was no statistically significant difference in VAS of pain between the two groups before analgesia ($P > .05$), but the VAS of pain in the EA group was significantly lower than the NEA group ($P < .05$) after analgesia or at delivery. The following outcomes showed no statistical difference between two groups: labor duration, postpartum hemorrhage, hemorrhage ≥ 500 mL, intrapartum injury, second days hemoglobin, C-reactive protein, antibiotic therapy days, hospitalizations days, and placenta residue ($P > .05$). The median hospitalization costs of EA group was 4697.5 yuan, and NEA group was 3673 yuan, the difference was statistically significant ($P < .001$). No adverse events related to EA occurred during hospitalization, only 3 patients showed mild lumbago and back pain after follow-up to three months postpartum, which was significantly relieved after proper rest.

Conclusion: EA can significantly reduce the pain of parturients, which may be effective and safe in the second-trimester induced labor.

Abbreviations: ASA = American Society of Anesthesiologists, BMI = body mass index, CRP = C-reactive protein, EA = epidural analgesia, non-EA (NEA) = no epidural analgesia, VAS = visual analog scale.

Keywords: epidural analgesia second, trimester induced labor

1. Introduction

Second-trimester induced labor was a measure in the 14 to 27^{+6} weeks due to a variety of factors forced termination of pregnancy, such as fetal anomalies, intrauterine fetal demise, maternal medical indications and elective termination. Second-trimester induced labor of pregnant women were often more likely to suffer from psychological and physiological double pain. In recent years, more and more scholars have paid attention to the severity of pain and its management during induction of labor. The nongovernmental NO Pain Labor & Delivery which was established and designed to educate Chinese women and their health care providers about the safe and effective use of labor analgesia had achieved significant achievements since 2008,[1] but the second-trimester induced labor of pregnant women received far less attention. Induction of labor in the second-trimester was different from the full-term pregnancy induced labor. When induced labor in the second-trimester, the

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cervix and lower uterine segment were immature, the labor duration was different, another the negative emotions of pregnant women, without considering the fetus, these factors also made the difference between second-trimester induced labor analgesia and full-term pregnancy analgesia. The analgesic management mode of labor induction in the second-trimester was controversial, and there were few studies on the application of epidural analgesia in the second-trimester induced labor, but the successful experience of labor epidural analgesia in full-term pregnancy was worth our reference. The study was to explore the feasibility of epidural analgesia technology in second-trimester induced labor.

2. Materials and Methods

2.1. Patients

Pregnant women who were admitted to the First Affiliated Hospital of Yangtze University for induced labor from January 2020 to December 2021 were included in the study. Inclusion criteria: Induced labor met the requirements of ethics and relevant laws, Age ≥ 18 years, Primipara, Gestational age was 16 to 27^{+6} weeks, No contraindications of epidural anesthesia, No contraindications for vaginal induction of labor, and American society of anesthesiologists (ASA) level I or II. Exclusion criteria: Stillbirth, Twin or multiple pregnancies, Mental disorders or cannot objectively describe symptoms and signs, Mifepristone and rivanol allergy or contraindication, and Neuraxial technique contraindication.

2.2. Study design

The study was a single-center, prospective, non-randomized, controlled study. This study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University (ky201901). This cohort study was registered at www.chictr.org.cn (ChiCTR2200056845). Written informed consent was obtained from all participants. The participants were divided into epidural analgesia (EA) group and no epidural analgesia (NEA) group according to their request in a 1:1 mode.

The use of EA in the second-trimester induced labor lacked corresponding guidelines, expert consensus, and even high-level evidence-based medical evidence support. In the study, we hypothesized that 60% to 70% of cervical canal regression was the analgesic time point. It was a bold attempt without precedent, mainly for the following reasons: the lower uterine segment was immature in second trimester, the evaluation of labor induction conditions in the second trimester cannot be completely referenced Bishop score, primipara labor usually begined with the cervical canal regression, followed by dilation of the uterine orifice, no need to consider the effect of anesthesia on the fetus, and reference the American College of Obstericians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine labor recommendations.

2.3. Procedures

The labor induction plan for both groups was as follows: on the first day, mifepristone was given orally 200 mg; On the second day, 100 mg Ethacridine Lactate was injected into the amniotic cavity through abdominal wall. The analgesic time point was set at 60% to 70% cervical canal regression, assessed by a senior midwife. The method of analgesia was epidural anesthesia. We administered the EA in the left lateral position at the L3-4 interspace for the parturients. This involved placing a epidural catheter through a 18-G epidural needle inserted into the epidural space. Firstly, we injected a test dose of 5 mL of 1% lidocaine and observed in 10 minutes, then we administered a bolus injected of a mixture of 0.075% ropivacaine + 0.25 μg/mL sufentanil and connected with a self-controlled EA pump. The EA pump administered ropivacaine and sufentanil mixture into the catheter to optimize pain relief. The type of maintenance protocol: patient controlled. We remove the catheter after the labor was completed. The NEA group didn't receive any systematic analgesia.

2.4. Study end points

The primary outcome: Degree and scores of pain before and after analgesic time point, including immediately before analgesic time point (P_1), half an hour after analgesic time point (P_2), one hour after analgesic time point (P_3) and delivery (P_4). Epidural analgesia related adverse events.

The secondary outcomes: Clinical parameter: postpartum hemorrhage (mL), hemorrhage ≥ 500mL (n), intrapartum injury, second days hemoglobin (g/L), C-reactive protein (CRP) (mg/L), antibiotic therapy (days), hospitalization days, hospitalization costs (yuan), placenta residue (n), and analgesia-related complications. Labor duration before and after analgesic time point, including from labor to analgesic time point (T1), from analgesic time point to delivery of fetus (T2), third-stage labor duration (T3), and total labor duration (T4).

Observation and follow-up to 3 months after labor induction.

The visual analog scale (VAS), ranging from 0 to 10 (a 10 cm line with endpoints labeled "on pain" and "most imaginable pain"), was used to measure pain.

Blood loss was measured by volumetric method and weighing method. Volumetric method: Blood was collected in a blood container during labor induction and then measured in a measuring cup. Weighing method: after induced labor, the weight of blood dressing and gauze was divided by 1.05 after subtracting the basic weight.

2.5. Sample size estimation and power analysis

Because this was a non-randomized study, we did not implement a sample size estimation. Utilizing the G*Power software package (http://www.gpower.hhu.de/), version 3.1.9.2, we instead performed a post hoc power analysis based on our results.

2.6. Statistical analysis

SPSS 21.0 (IBM, Armonk, NY) software was used for statistical analyses. Continuous variables was described as mean ± standard deviation when normally distributed or median (25th–75th percentile) [M(P25–P75)] when non-normally distributed. According to the distribution we compared continuous variables using 2-tailed Student *t* test or Wilcoxon signed rank test for two groups. Categorical variables were described as numbers (percentages) and compared using the χ^2 or Fisher exact tests. *P* value < 0.5 was considered statistically significant.

3. Results

From January 1, 2020 to December 31, 2021, a total of 60 patients who met the clinical trial criteria were identified and underwent assignment, of the 30 patients assigned to the EA group and 30 to NEA group. Vaginal induction of labor was successful in both groups. There were no statistical significant difference in Age, Body mass index (BMI), Gravidity, Fetal double parietal diameter, Fetal femur length, Gestational age and hemoglobin between the two groups ($P > .05$) (Table 1).

About the VAS of pain, there was no statistical difference in VAS of immediate pain between the two groups before analgesia ($P > .05$), but the VAS of pain after analgesia in the EA group was significantly lower than the NEA group ($P < .05$), whether it was half an hour after analgesia, 1 hour after analgesia and delivery (Table 2).

Table 1

Comparison of general clinical characteristics of pregnant women between the two groups.

	EA group	NEA group	Statistics	*P* value
Age (yr)	27.4 ± 5.6	26.4 ± 4.2	$t = 0.782$	.438
BMI	25.1 (23.3–25.6)	24.5 (23.3–25.7)	$Z = -0.178$	.859
Gravidity	2 (1–2)	1 (1–3)	$Z = -0.113$	.910
Double parietal (mm)	51.7 ± 7.3	48.4 ± 9.0	$t = 1.612$	.112
Femur length (mm)	35.2 ± 6.0	32.8 ± 7.6	$t = 1.330$	.189
Gestational age (d)	155.3 ± 18.2	151 ± 22.4	$t = 0.735$	.465
Hemoglobin (g/L)	109.6 ± 10.3	108.7 ± 9.6	$t = 0.364$	.717

BMI = body mass index, EA = epidural analgesia, NEA = no epidural analgesia.

Table 2

Comparison of VAS of pain before and after analgesia between two groups.

	EA group	NEA group	Statistics (*Z*)	*P* value
P_1	4 (3–5)	4 (3–5)	–0.607	.544
P_2	2 (2–3)	5 (5–6)	–6.718	<.001
P_3	2 (1–2)	7 (6–7)	–6.815	<.001
P_4	1 (1–2)	8 (8–9)	–6.867	<.001

EA = epidural analgesia, NEA = no epidural analgesia, P_1 = VAS of pain before analgesic time point, P_2 = VAS of pain half an hour after analgesic time point, P_3 = VAS of pain one hour after analgesic time point, P_4 = VAS of pain delivery, VAS = visual analog scale.

In the EA group, the labor duration from labor to analgesia point (T_1) was 237 (123.8–392.8) minutes, the labor duration from analgesia point to delivery (T_2) was 249 (138.3–308.5) minutes, and the third labor duration (T_3) was 5.2 ± 1.8 minutes, the total labor duration (T_4) was 547.6 ± 259.1 minutes. In the NEA group, T_1 was 184 (132–354.5) minutes, T_2 was 197 (146.5–266) minutes, T_3 was 5 ± 1.9 minutes, and T_4 was 457.4 ± 167.8 minutes. There was no statistically significant difference in labor duration T1, T2, T3, or T4 between two groups ($P > .05$) (Table 3).

About the secondary outcomes, there was no statistical difference in postpartum hemorrhage between the two groups ($P = .762$), and there was 1 case postpartum hemorrhage of more than 500 mL in each group, which returned to normal after uterine contractions, hemostasis and blood transfusion. There were no statistical difference in second days hemoglobin, CRP, antibiotic therapy days and hospitalization days between the two groups ($P > .05$). There were 4 cases of soft birth canal injury in EA group and 5 cases of soft birth canal injury in NEA group, all of which were *I°* perineal laceration, and the difference was not statistically significant ($P > .05$). The median hospitalization cost of EA group was 4697.5 yuan, and the NEA group was 3673 yuan, the difference was statistically significant ($P < .001$), but there was no significant difference in hospitalization cost between the two group after excluding anesthesia cost ($P > .05$). Color doppler ultrasonography was performed on all patients half a month after labor induction. In the EA group, there were 7 (21.9%) patients with residual ultrasonography, and all received conservative drug treatment. One month after oral drug treatment, color doppler ultrasonography showed no abnormalities. In the NEA group, color doppler ultrasonography indicated 8 (26.7%) cases of residue, only 1 case needed uterine clearing operation, and the rest received conservative drug treatment, color doppler ultrasonography showed normalities after one month, there was no statistical difference between the two groups ($P > .05$) (Table 4).

Table 3

Comparison of labor duration between two groups.

	EA group	NEA group	Statistics	*P* value
T_1 (min)	237 (123.8–392.8)	184 (132–354.5)	$Z = -0.651$	.515
T_2 (min)	249 (138.3–308.5)	197 (146.5–266)	$Z = -1.338$	.181
T_3 (min)	5.23 ± 1.79	5 ± 1.91	$t = 0.487$	.628
T_4 (min)	547.6 ± 259.1	457 ± 167.8	$t = 1.601$	.115

EA = epidural analgesia, NEA = no epidural analgesia, T_1 = from labor to analgesia point, T_2 = from analgesia point to delivery, T_3 = the third labor duration, T_4 = the total labor duration.

There was no negative emotional impact from EA during follow-up after labor induction, and patients were psychologically receptive to EA. In addition, according to data analysis and questionnaire, EA can not only relieve the pain, but also to a certain extent eliminate the patient's nervous and anxious mood. Observation and follow-up of analgesia related adverse events. In the EA group, no adverse events related to analgesia occurred during hospitalization, and the patients were followed up to 3 months after labor induction. During the follow-up period, only 10% (3/30) patients showed mild low back pain at early stage, which was significantly relieved after proper rest. NEA patients had no other discomfort except for residual ultrasonography during follow-up, who returned to normal after treatment.

4. Discussion

As we all know, labor analgesia technology was first used in obstetrics practice in 1946.[2] At present, with the gradual opening of China's three-child policy, labor analgesia technology was used more and more frequently to meet the physiological and psychological needs of pregnant women. Among labor analgesia technology, epidural analgesia was considered as the most effective analgesic mode.[2–5] Epidural analgesia was mainly used for full-term pregnancy delivery, and its safety has been widely recognized, but its influence on labor duration, pregnant women, fetuses and neonates were still controversial.[3,6,7] As a minority special group, women in the second-trimester will also suffer from various pains during labor induction, which need to be paid enough attention by their health care provided. It was equally important to strengthen pain management during labor induction in the second trimester. Compared with full-term pregnancy, the fetus was not considered in the second-trimester induced labor, which may make the application of epidural analgesia technology in the second-trimester induced labor more leisurely. However, there were few studies on the application of epidural analgesia technology in the second-trimester induced labor, and the optimal analgesic mode for the second-trimester induced labor had not been determined.[8–11] Based on the particularity of labor induction in the second trimester, and referring to the painless delivery of full-term pregnancy, we boldly tried to use epidural analgesia technology in the second-trimester induced labor, and set the analgesia time point in the cervical canal regression 60% to 70%.

In the study, we found that parturients administered EA exhibited a significant decrease in the VAS score of pain, which

Table 4

Comparison of postpartum related clinical indicators between the two groups.

	EA group	NEA group	Statistics	*P* value
Postpartum hemorrhage (mL)	141.5 (111.5–160.5)	139.5 (123.5–164.8)	$Z = -0.303$	.762
Hemorrhage ≥ 500 mL (n)	1	1	$X = 0$	1
Intrapartum injury (n)	4 (13.3%)	5 (15.7%)	$X = 0.131$	.718
Second days hemoglobin (g/L)	101 ± 9.2	101 ± 10.3	$Z = -0.026$	.979
CRP (mg/L)	35.8 (16.4–50.2)	34.9 (27–51.1)	$Z = -0.177$	.859
Antibiotic therapy (d)	2 (2–3)	2 (2–2)	$Z = -1.413$	.158
Hospitalizations days	5 (5–6)	6 (5–7)	$Z = -1.1$	.271
Hospitalizations costs (yuan)	4967.5 (4756–5872.3)	3673 (3216.3–4104.5)	$Z = -4.997$	<.001
Placenta residue (n)	7 (23.3%)	8 (26.7%)	$X = 0.089$	.766

CRP = C-reactive protein, EA = epidural analgesia, NEA = no epidural analgesia.

indicated the effectiveness of EA in labor pain relief. According to the 2019 guidelines for obstetric analgesia and anesthesia issued by the American College of Obstetricians and Gynecologists, epidural analgesia was the gold standard for labor analgesia.[5] Anim-somuah and Nanji et al[3,12] also showed that epidural analgesia can significantly relieve labor pain. At present, there was still some controversy about the effect of epidural analgesia on the labor duration of full-term pregnancy, and the optimal initiation time was also lack of unified standards.[13–17] Zha et al[18] found that epidural analgesia administered before a cervical dilation of 6cm may prolong the total, first- and second-stages labor duration. However, Wang et al[16] meta-analysis showed that low concentration of local anesthesia for epidural analgesia did not prolong duration of the second stage of labor. In the second-trimester induced labor, whether epidural analgesia had an impact on the labor duration, and the choice of the optimal epidural analgesia initiation time, there was a lack of relevant expert opinions, and even lacked of relevant literature reports. In the study, we tried to set the epidural analgesia initiation time in the cervical canal regression 60% to 70%, and we found that there was no statistically significant difference in labor duration between EA group and NEA group regardless of T1, T2, T3, or T4 stage. It may be seen that epidural analgesia did not affect the labor duration in the second trimester induced labor.

In the analysis of secondary indicators, we found that there was no statistical difference in postpartum hemorrhage, intrapartum injury, CRP, antibiotic therapy days, placental membrane residue, and hospitalization days between EA and NEA group, which indicate that EA did not increase the additional treatment burden in the process of labor induction. In addition, there were no EA-related complications in the EA group during the whole process of labor induction, and only 3 patients had mild lumbar and back discomfort during follow-up after labor induction, which were significantly relieved after proper rest. At a review half a month after induced labor, the residual ultrasonography was no statistical difference between the two groups. In general, epidural analgesia techniques may be safety in second-trimester induced labor. As for the treatment cost, the overall treatment cost of EA group was significantly higher than NEA group, but there was no statistically significant difference in the treatment cost between the two groups after deducting the anesthesia related costs. In view of the increase of China's annual per capital disposable income level and the popularity of commercial medical insurance, patients can fully afford the anesthesia related costs.

We explored the feasibility of EA technology in the second-trimester induced labor from a prospective perspective, in order to obtain high quality evidence. The trail had obvious limitations. Firstly, the study was a single-center, non-randomized controlled study, which will affect the number of cases enrolled and the experimental results may be biased. Secondly, the sample size was limited, which was not sufficiently convincing to evaluate the efficacy and safety of epidural analgesia in second-trimester induced labor. Thirdly, VAS score of pain may be affected by subjective factors of patients, which may bias the results of analgesia for pain relief. Fourth, the analgesic time point was set at cervical canal regression 60% to 70%, some parturients in EA group asked for EA administration early, it would be unethical to delay this pain relief.

In conclusion, epidural analgesia can significantly relieve second-trimester labor pain, and has fewer side effects. It can be seen that epidural analgesia technique was feasible in the second-trimester induced labor.

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Author contributions

YZ and K-MC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. Conception and design: YZ, Y-HZ and K-MC. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: YZ and Y-HZ. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: YZ, Y-HZ, and X-FZ. Supervision: K-MC. All authors read and approved the final manuscript.

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References

[1] Hu LQ, Flood P, Li Y, et al. No pain labor & delivery: a global health initiative's impact on clinical outcomes in China. Anesth Analg. 2016;122:1931–8.

[2] Aragão FF, Aragão PW, Martins CA, et al. Analgesia de parto no neuroeixo: uma revisão da literatura [Neuraxial labor analgesia: a literature review] [in Portuguese]. Braz J Anesthesiol. 2019;69:291–298.

[3] Anim-Somuah M, Smyth RM, Cyna AM, et al. Epidural versus non-epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev. 2018;5:CD000331.

[4] Howell CJ, Kidd C, Roberts W, et al. A randomised controlled trial of epidural compared with non-epidural analgesia in labour. BJOG. 2001;108:27–33.

[5] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin No. 209: obstetric analgesia and anesthesia. Obstet Gynecol. 2019;133:e208–25.

[6] Bos EME, Hollmann MW, Lirk P. Safety and efficacy of epidural analgesia. Curr Opin Anaesthesiol. 2017;30:736–42.

[7] Morton S, Kua J, Mullington CJ. Epidural analgesia, intrapartum hyperthermia, and neonatal brain injury: a systematic review and meta-analysis. Br J Anaesth. 2021;126:500–15.

[8] Hamoda H, Ashok PW, Flett GM, et al. Analgesia requirements and predictors of analgesia use for women undergoing medical abortion up to 22 weeks of gestation. BJOG. 2004;111:996–1000.

[9] Jackson E, Kapp N. Pain control in first-trimester and second-trimester medical termination of pregnancy: a systematic review. Contraception. 2011;83:116–26.

[10] Hamer T, Deverman S, Nunes KJ, et al. Pain and analgesia during labor and delivery between 16 0/7 and 22 6/7 weeks of gestation. Obstet Gynecol. 2016;127:1161–5.

[11] Jackson E, Kapp N. Pain management for medical and surgical termination of pregnancy between 13 and 24 weeks of gestation: a systematic review. BJOG. 2020;127:1348–57.

[12] Nanji JA, Carvalho B. Pain management during labor and vaginal birth. Best Pract Res Clin Obstet Gynaecol. 2020;67:100–12.

[13] Wong CA, Scavone BM, Peaceman AM, et al. The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. N Engl J Med. 2005;352:655–65.

[14] Ohel G, Gonen R, Vaida S, et al. Early versus late initiation of epidural analgesia in labor: does it increase the risk of cesarean section? A randomized trial. Am J Obstet Gynecol. 2006;194:600–5.

[15] Sng BL, Leong WL, Zeng Y, et al. Early versus late initiation of epidural analgesia for labour. Cochrane Database Syst Rev. 2014:CD007238.

[16] Wang TT, Sun S, Huang SQ. Effects of epidural labor analgesia with low concentrations of local anesthetics on obstetric outcomes: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg. 2017;124:1571–80.

[17] Wang F, Shen X, Guo X, et al.; Labor Analgesia Examining Group. Epidural analgesia in the latent phase of labor and the risk of cesarean delivery: a five-year randomized controlled trial. Anesthesiology. 2009;111:871–80.

[18] Zha Y, Gong X, Yang C, et al. Epidural analgesia during labor and its optimal initiation time-points: a real-world study on 400 Chinese nulliparas. Medicine (Baltim). 2021;100:e24923.