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Effects of a single epidural injection of low-dose esketamine on perioperative sedation and analgesia during cesarean section

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Abstract: Objective To evaluate the analgesic and sedative effect of single epidural application of esketamine in cesarean section during perioperative period, and analyze the clinical application value of esketamine in cesearean section epidural analgesia and sedation. **Methods** From October 2021 to March 2022, 100 patients undergoing lower segment cesarean section under combined spinal epidural anesthesia in Rugao Hospital Affiliated to Nantong University were selected and randomly divided into morphine group (n=50) and esketamine group (n=50). After delivery of newborns (Apgar score ⩾ 8) and removal of the umbilical placenta for 5 min, individuals in esketamine group were administered 20 mg ketamine, 5 mg dexamethasone plus 9 mg ropivacaine via an epidural catheter diluted with 0.9% sodium chloride to 6 mL; while individuals in morphine group were administered 2 mg morphine, 5 mg dexamethasone plus 9 mg ropivacaine via an epidural catheter, diluted with the same volume (6 mL) of sodium chloride. The VAS score and Ramsay score at different time points after epidural administration, postoperative supplemental analgesic use and adverse reactions of the two groups were recorded. **Results** There was no significant difference between the two groups in VAS scores at 5 min after epidural administration, at the end of operation, 24 h after operation, and 48 h after operation, as well as the time of first use of supplementary analgesic drugs after operation and the proportion of the number of people (P>0.05). At 5 min after epidural administration, Ramsay scores in esketamine group were significantly higher than those in morphine group (P<0.05), and that there was no statistically difference in Ramsay scores between the two groups after surgery (P>0.05). The incidence of dysuria (22.00% *vs* 4.00%, χ^2=7.162, P<0.05) and pruritus (18.00% *vs* 0, χ^2 =7.814, P<0.05) in morphine group were higher than those in esketamine group. **Conclusion** Esketamine and morphine both exert effective analgesic effects during the perioperative period of cesarean section, and more importantly, ketamine is superior to morphine in sedative effect during cesarean section and reducing postoperative adverse reactions.

Keywords: Esketamine; Morphine; Cesarean section; Analgesia; Sedation; Epidural anesthesia

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When a puerpera undergoes cesarean section, perioperative visceral pulling, peritoneal irritation, skin incision, and uterine contraction may cause acute pain. If the pain is poorly controlled, the persistent pain excites the neurons in the posterior horn of the spinal cord of the central nervous system, and N-methyl-D-aspartate (NMDA) receptors are activated, and ultimately, the severe acute pain is transformed into chronic post-surgery pain (CPSP) [1-2]. Perioperative analgesia can prevent the occurrence of chronic post-surgical pain, which is consistent with the theory of accelerated postoperative recovery advocated in current clinical practice. Combined lumbar-epidural anesthesia has a good anesthetic effect, and also can provide a good way for postoperative analgesia by leaving a tube in the epidural cavity [3]. Compared with ketamine, esketamine has a stronger analgesic effect and fewer side effects, and its potency strength is 2-4 times higher than that of ketamine, which not only reduces perioperative opioid use, but also has potential neuroprotective effects [4-6]. This study aims to evaluate the perioperative analgesic and sedative effects of single epidural application of esketamine in cesarean delivery and to analyze the clinical value of esketamine in epidural analgesia and sedation in cesarean delivery.

1 Material and methodology

1.1 General information

This study was a double-blind randomized controlled trial, which had been approved by the Ethics Committee of Rugao Hospital Affiliated to Nantong University (Ethics Approval No.: KY20230101). The consent of all the puerperas and their families who participated in the trial was obtained. One hundred cases of patients who underwent lower uterine segment cesarean section under combined lumbar and rigid anesthesia in Rugao Hospital affiliated to Nantong University from October 2021 to March 2022 were selected for the study.

Inclusion criteria: (1) puerperas with full-term pregnancy, single birth, age 19-42 weeks old, body mass index (BMI) of 24-35 kg/m^2 , ASA II. (2) the proposed mode of anesthesia was combined lumbar and rigid anesthesia, and agreed to a single epidural administration for postoperative analgesia.

Exclusion criteria: (1) preoperative fetal heart abnormalities, gestational hypertension, gestational diabetes mellitus and other obstetric complications, combined important organ dysfunction, gynecological diseases and tumors; (2) contraindications or allergies to the test drugs; (3) contraindications to intrathecal anesthesia, such as puncture site infections, coagulation disorders, etc.; (4) history of use of the test-related drugs in the past 6 months; (5) history of psychiatric disorders or chronic pain; (6) Motion sickness, or preoperative nausea or vomiting; (7) Patients with pruritus due to pregnancy or other diseases.

Elimination criteria: (1) poor effect of combined lumbar and rigid anesthesia, anesthesia plane higher than L_4 and lower than L_8, poor epidural placement, blood or cerebrospinal fluid in the epidural tube retraction, etc.; (2) unstable vital signs, nausea and vomiting, chest tightness and palpitation, dizziness and lightheadedness of puerperas within 5 min after the delivery of the fetus.

1.2 Grouping

Puerperas who were eligible for the study were divided into the esketamine group and morphine group, 50 cases in each group, in the order of cesarean section operation by random number table method. There was no statistically significant difference between the two groups when comparing the general clinical data such as maternal age, BMI, and number of deliveries (P>0.05) **[Table 1]**. Esketamine group: esketamine 20 mg + ropivacaine 9 mg + dexamethasone 5 mg + saline to 6 mL; Morphine group: morphine 2 mg + ropivacaine 9 mg + dexamethasone 5 mg + saline to 6 mL.

Tab.1 Comparison of general clinical data between two groups [n=50, M (P_{25} , P_{75})]

Groups	Age (years, $\bar{x}\pm s$)	BMI (kg/m^2)	Production numbers
Morphine group	29.67±3.79	28.44 (27.40, 30.36)	2 (1, 2)
Aceketamine group	30.62±4.87	28.90 (28.04, 30.72)	2 (1, 2)
***t/Z* value**	1.109	0.893	0.608
***P* value**	0.274	0.372	0.543

1.3 Anesthesia methods

All particpants in the trial did not take preoperative drugs before entering the operating room. After entering the operating room, the multifunctional monitor was connected to routinely monitor the electrocardiogram, blood pressure, heart rate, pulse oximetry. Non-rebreather mask was adapted and the venous channel was open with about 300 mL of saline rapidly dripped in. The woman was in the left side of the thoracic-knee position, positioning the L_{2-3} vertebral space and marking, iodine-vodine disinfection, laying the hole towel. After puncturing the L_{2-3} vertebral space and entering the epidural, and placing the lumbar anesthesia needle through the epidural needle, the cerebrospinal fluid was seen, and the syringe with bupivacaine was connected to pump back the cerebrospinal fluid and dilute it to 2.5 mL, and then according to the weight and height of the puerpera, 12-15 mg of bupivacaine was slowly injected into the subarachnoid space, and then the lumbar anesthesia needle was withdrawn, and then an epidural catheter was placed cephalad through the epidural needle and the catheter was retained in the catheter for 3.5 cm, and then pumped back to be free of blood and cerebrospinal fluid. After fixing the epidural catheter, the puerpera was instructed to lie flat, and the operating bed was tilted to the left side at about 20 degrees. After 5 min, the blocking plane of intradural anesthesia was measured at the level of T_6, not higher than the level of T_4, and not lower than the level of T_8. During the operation, no sedative or analgesic was used intravenously. When the maternal SBP was <90 mmHg or the blood pressure dropped by more than 30% of the basal blood pressure, ephedrine hydrochloride injection of 6 mg or phenylephrine hydrochloride injection of 100 ug was injected to correct the condition, and it was repeated if necessary; when the heart rate was <50 bpm, atropine sulfate injection of 0.25 mg was injected, and it was repeated if necessary. After the fetus was delivered for 5 min, the anesthesiologist injected the analgesic formula via epidural, and the epidural catheter was removed at the end of the operation and sent back to the ward. When the postoperative visual analog scale (VAS) score > 5, oral ibuprofen capsule 0.2 g was given to the patients for remedy analgesia.

1.4 Observation indexes

Primary indexes: recording the VAS scores of the women in the two groups at 5 min after epidural administration, the end of operation, 24 h postoperatively and 48 h postoperatively and the use of postoperative supplemental analgesics in the two groups, recording the Ramsay scores of the women in the two groups at 5 min after epidural administration and at the end of operation.

Secondary indicators: perioperative maternal nausea and vomiting, dizziness and lightheadedness, hallucinations, nightmares, diplopia, urinary and defecation difficulties, itchy skin and other adverse reactions in both groups.

1.5 Statistics Methods

The test efficacy analysis by PASS 11.0 showed that the efficacy of this study's sample size for the test of between-group differences reached 100% at the 5% significance level. SPSS 21.0 software was used to analyze the data, and the measurement data were first tested by

Kolmogorov-Smirnova test, and if they conformed to the normal distribution, they were expressed as $\bar{x}\pm s$, and comparisons were made by independent samples t-tests. Count data were expressed as case (%), and comparisons between groups were made using the chi-square test or the Fisher exact test. $P < 0.05$ was considered a statistically significant difference.

2 Results

2.1 VAS scores at different time points

There was no statistically significant difference in maternal VAS scores between the two groups at 5 min after epidural administration, the end of the procedure, 24 h postoperatively, and 48 h postoperatively (P>0.05) **[Table 2]**.

2.2 Postoperative supplemental analgesic medication

The difference between the time of the first postoperative use of supplemental analgesic medication and the percentage of the number of people in the two groups was not statistically significant (P>0.05) **[Table 3].**

2.3 Ramsay score

At 5 min after epidural push, the sedation score of the esketamine group was significantly higher than that of the morphine group (P<0.05). At the end of the operation, the difference in sedation scores between the two groups was not statistically significant (P>0.05) **[Table 4]**.

2.4 Adverse reactions

There was no statistically significant difference in the incidence of nausea and vomiting, dizziness and lightheadedness, hallucinations, nightmares and diplopia between the two groups (P>0.05). The incidence of urinary and faecal difficulties and itching of the skin in the morphine group was higher than that in the esketamine group (P<0.05) **[Table 5].**

Tab.2 Comparison of the maternal VAS scores between two groups [n=50, M (P_{25} , P_{75})]

Groups	Administer for 5 min	Postoperative period	24 h after surgery	48 h after surgery
Morphine group	0 (0,0)	0 (0,0)	3 (3,3)	1.5 (1,2)
Esketamine group	0 (0,0)	0 (0,0)	3 (3,4)	2 (1,2)
F/P_{time} value	1 473.294/<0.001			
F/P_{group} value	2.992/ 0.084			
$F/P_{interaction}$ value	0.998/ 0.394			

Tab.3 Comparison of postoperative supplementary analgesic medication between two groups (n=50)

Groups	Time to first dose (h, $\bar{x}\pm s$)	Medication used [case (%)]
Morphine group	10.42±6.18	6 (12.00)
Esketamine group	12.80±5.81	5 (10.00)
t/χ^2 value	1.984	0.102
P value	0.051	0.749

Tab.4 Comparison of maternal Ramsay scores between two groups [n=50, M (P_{25} , P_{75})]

Groups	Administer for 5 min	Postoperative period
Morphine group	2 (2,2)	2 (2,2)
Esketamine group	2 (2,3)	2 (2,2)
Z value	2.499	0.980
P value	0.012	0.327

Tab.5 Occurrence of adverse reactions in pregnant women in both groups [n=50, cases (%)]

Groups	Nausea and vomiting	Dizziness	Hallucinations, nightmares and diplopia	Urinary and faecal difficulties	Pruritus
Esketamine group	5 (10.00)	9 (18.00)	4 (8.00)	2 (4.00)	0
Morphine group	9 (18.00)	6 (12.00)	0	11 (22.00)	9 (18.00)
χ^2 value	1.329	0.706	2.344	7.162	7.814
P value	0.249	0.401	0.126	0.007	0.005

3 Discussion

The proportion of scarred uterus and advanced maternal age has increased in recent years, and safe and comfortable postoperative analgesia has become a common concern [7]. In this study, all the women chose combined spinal-epidural anesthesia, and the epidural catheter had been pre-positioned in the epidural. Single epidural analgesia has the advantages of simplicity and convenience, low cost, can get out of bed earlier, no infection following consistant epidural indwelling catheters, neurological complications, anticoagulation, catheter fracture, detachment, respiratory depression, and the limited early out of bed activities. The results of this study show that a single epidural injection of esketamine can provide good intraoperative sedation and postoperative analgesia, with fewer adverse effects.

The mechanism of epidural analgesia of esketamine may be at these 4 sites of action: (1) esketamine is a NMDA receptor in the central nervous system, and the main mechanism by which it produces systemic anesthesia and analgesia is to block the excitatory nerve conduction of the NMDA receptor. The NMDA receptors are mainly distributed in the brain and spinal cord. After epidural

injection of esketamine, it enters the subarachnoid space through diffusion and blocks the NMDA receptors in the spinal cord, and then circulates to the intracranium through the cerebrospinal fluid, and acts on the NMDA receptors in the brain; (2) esketamine binds with the opioid receptor in the brain and spinal cord, and excites the opioid receptor, and esketamine has a certain agonism of opioid μ-receptor [8]; (3) Esketamine has a significant local anesthetic effect on the spinal cord and peripheral nerves by blocking the electronically controlled sodium channels, but its local anesthetic effect is weak, and the use of large doses of general anesthesia will mask the effect of local anesthesia [9]; (4) Esketamine has a strong anti-inflammatory effect, and it has been pointed out in a study [10] that esketamine can significantly reduce the levels of inflammatory factors (IL-6 and IL-8), and elevate the levels of the anti-inflammatory factor (IL-10). Esketamine has been shown to be safe for use in cesarean section anesthesia [11], and the dose used is directly proportional to the incidence of postoperative psychiatric states such as hallucinations, nightmares, and agitation, making the use of subthreshold doses a desirable dosing regimen. A previous study [12] showed that epidural injection of 0.25 mg/kg of esketamine in combination with local anesthetics resulted in better analgesia, and the study also observed that intrathecal use of esketamine had a compensatory sympathomimetic activity with little or no systemic effect.

In this study, epidural injection of esketamine showed a postoperative analgesic effect similar to that of morphine, but morphine has a longer duration of action, which may be due to the lipophilic nature of esketamine and its shorter duration of action. Epidural injection of esketamine has better intraoperative sedation effect because esketamine has the characteristics of high lipid solubility and low protein binding rate, which can easily pass the blood-brain barrier or enter the brain through the cerebrospinal fluid to produce a sedative effect [13]. After epidural administration of water-soluble morphine, a very small amount of morphine enters the brain through the blood-brain barrier or through the cerebrospinal fluid, and the puerperas can coordinate the treatment and a certain degree of orientation [14], which is consistent with the results of the present study. In addition, the incidence of maternal nausea and vomiting in the morphine group was slightly higher than that in the esketamine group, and the incidence of adverse reactions of dizziness and lightheadedness, hallucinations, nightmares, and hallucinations in the esketamine group was slightly higher than that in the morphine group. The difference in the incidence of postoperative urinary and defecation difficulties and itching between the two groups was statistically significant, suggesting that the epidural injection of esketamine has a significant advantage over morphine for postoperative analgesia.

There are many foreign reports on the use of esketamine in epidural application. Animal experiments and clinical trials have confirmed that the same dose of esketamine administered epidurally can achieve stronger analgesic effect compared with intravenous administration [7]. The combination of esketamine and local anesthetics for intrathecal use can significantly prolong the duration of analgesia, improve analgesic scores, and reduce the use of analgesic drugs [7]. Feltracco *et al.* [15] enrolled 140 patients who underwent single lung resection, and administered a subnarcotic dose of esketamine by intraoperative continuous epidural infusion to observe the analgesic effect of post-thoracotomy pain. The results showed that the epidural infusion of a subanesthetic dose of esketamine had a better postoperative analgesic effect compared with ropivacaine. Wang *et al.* [16] investigated the effect of subthreshold dosage of esketamine on the effect of combined lumbar and rigid block in elderly hip arthroplasty patients through a randomized controlled trial, and pointed out that subthreshold dosage of esketamine injected into the epidural cavity could keep the hemodynamics of the patients relatively stable after anesthesia, significantly prolong the duration of analgesia, and reduce the postoperative pain score, improve the analgesic effect in the early postoperative period, and did not increase the incidence of adverse reactions.

There are still very few studies on esketamine in epidural. In this study, we found that a single application of esketamine in epidural has good postoperative analgesia, better intraoperative sedation, and fewer side effects, but the exact mechanism of its action is still not clear. In future studies, the author will address the above problems, add objective indicators, increase the sample size, and continue to explore the optimal dosage of epidural application of esketamine to provide reference for clinical use.

In conclusion, single epidural application of esketamine and morphine had good analgesic effect on perioperative cesarean delivery, both of them had no adverse effect on the time of the first breastfeeding, and there was no significant difference in patient satisfaction, and the single epidural application of esketamine was better than morphine in terms of the effect of intraoperative sedation for cesarean delivery and the reduction of the occurrence of postoperative adverse reactions. Single epidural injection of esketamine is a better choice for postoperative analgesia after cesarean section, especially for primary hospitals, it is simple to operate, safe and reliable, with fewer side effects and low cost.

Conflict of interest None

Reference

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·论　著·

单次硬膜外注射小剂量艾司氯胺酮对剖宫产围术期镇静镇痛的影响

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摘要：目的　对硬膜外单次应用艾司氯胺酮在剖宫产在围术期镇痛镇静效果进行评估，并分析其在剖宫产硬膜外镇痛镇静的临床应用价值。**方法**　选择 2021 年 10 月至 2022 年 3 月南通大学附属如皋医院腰硬联合麻醉下行子宫下段剖宫产术产妇 100 例为研究对象，随机分为吗啡组和艾司氯胺酮组，各 50 例。在新生儿（Apgar 评分≥8 分）娩出，断脐胎盘取出 5 min 后，艾司氯胺酮组经硬膜外导管给予艾司氯胺酮 20 mg+地塞米松 5 mg+罗哌卡因 9 mg 用 0.9%氯化钠稀释至 6 mL；吗啡组经硬膜外导管给予吗啡 2 mg+地塞米松 5 mg+罗哌卡因 9 mg 用 0.9%氯化钠稀释至 6 mL。记录两组硬膜外给药后不同时间点产妇的 VAS 评分、Ramsay 评分、术后补充镇痛药使用情况及不良反应。**结果**　两组在硬膜外给药后 5 min、术毕时、术后 24 h 和术后 48 h 的 VAS 评分，术后首次使用补充镇痛药物的时间以及人数占比差异无统计学意义（$P>0.05$）。硬膜外给药后 5 min 艾司氯胺酮组 Ramsay 评分高于吗啡组（$P<0.05$），术毕两组 Ramsay 评分差异无统计学意义（$P>0.05$）。大小便困难（22.00% *vs* 4.00%，$\chi^2=7.162$，$P<0.05$）及皮肤瘙痒（18.00% *vs* 0，$\chi^2=7.814$，$P<0.05$）发生率吗啡组高于艾司氯胺酮组。**结论**　艾司氯胺酮与吗啡单次硬膜外应用在剖宫产围术期均有良好的镇痛效果，且艾司氯胺酮单次硬膜外应用对剖宫产术中镇静效果及减少术后不良反应发生方面优于吗啡。

关键词：艾司氯胺酮；吗啡；剖宫产；镇痛；镇静；硬膜外麻醉

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Abstract: Objective　To evaluate the analgesic and sedative effect of single epidural application of esketamine in cesarean section during perioperative period, and analyze the clinical application value of esketamine in cesarean section epidural analgesia and sedation. **Methods**　From October 2021 to March 2022, 100 patients undergoing lower segment cesarean section under combined spinal epidural anesthesia in Rugao Hospital Affiliated to Nantong University were selected and randomly divided into morphine group ($n=50$) and esketamine group ($n=50$). After delivery of newborns (Apgar score ≥ 8) and removal of the umbilical placenta for 5 min, individuals in esketamine group were administered 20 mg ketamine, 5 mg dexamethasone plus 9 mg ropivacaine via an epidural catheter diluted with 0.9% sodium chloride to 6 mL; while individuals in morphine group were administered 2 mg morphine, 5 mg dexamethasone plus 9 mg ropivacaine via an epidural catheter, diluted with same volume (6 mL) of sodium chloride. The VAS score and Ramsay

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score at different time points after epidural administration, postoperative supplemental analgesic use and adverse reactions of the two groups were recorded. **Results** There was no significant difference between the two groups in VAS scores at 5 min after epidural administration, at the end of operation, 24 h after operation, and 48 h after operation, as well as the time of first use of supplementary analgesic drugs after operation and the proportion of the number of people ($P>0.05$). At 5 min after epidural administration, Ramsay scores in esketamine group were significantly higher than those in morphine group ($P<0.05$), and that there was no statistically difference in Ramsay scores between the two groups after surgery ($P>0.05$). The incidence of dysuria (22.00% *vs* 4.00%, $\chi^2=7.162$, $P<0.05$) and pruritus (18.00% *vs* 0, $\chi^2=7.814$, $P<0.05$) in morphine group were higher than those in esketamine group. **Conclusion** Esketamine and morphine both exert effective analgesic effects during the perioperative period of cesarean section, and more importantly, ketamine is superior to morphine in sedative effect during cesarean section and reducing postoperative adverse reactions.

Keywords: Esketamine; Morphine; Cesarean section; Analgesia; Sedation; Epidural anesthesia

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剖宫产围术期内脏牵拉、腹膜刺激、皮肤切口、子宫收缩等均会引起急性疼痛，如疼痛控制不佳，持续的疼痛兴奋中枢神经系统脊髓后角的神经元，N-甲基-D-天冬氨酸（N-methyl-D-aspartic acid，NMDA）受体被激活，最终严重的急性疼痛转为慢性术后疼痛（chronic post-surgery pain，CPSP）[1-2]。良好的围术期镇痛可以预防慢性术后疼痛的发生，这与目前临床上提倡的加速康复外科理论一致。腰硬联合麻醉拥有良好的麻醉效果，同时还可以在硬膜外腔留管为术后镇痛提供良好的途径[3]。与氯胺酮相比，艾司氯胺酮的镇痛效果更强、副作用更少，其效价强度是氯胺酮的 2~2.5 倍，不仅可减少围术期阿片类药物的使用量，还具有潜在的神经保护作用[4-6]。本研究对硬膜外单次应用艾司氯胺酮在剖宫产围术期镇痛镇静效果进行评估，分析艾司氯胺酮在剖宫产硬膜外镇痛镇静的临床应用价值。

1　资料与方法

1.1　一般资料　本研究为双盲随机对照试验，已通过南通大学附属如皋医院伦理委员会批准（伦理批号：KY20230101），同时取得所有参加本试验的产妇及家属的同意并签署知情同意书。选择 2021 年 10 月至 2022 年 3 月在南通大学附属如皋医院拟于腰硬联合麻醉下行子宫下段剖宫产术的产妇 100 例为研究对象。入选标准：（1）产妇足月妊娠，单胎，年龄 19~42 周岁，BMI 为 24~35 kg/m^2，ASA 分级Ⅱ级。（2）拟定麻醉方式为腰硬联合麻醉，且同意单次硬膜外给药用于术后镇痛。排除标准：（1）术前胎心异常、妊高压、妊娠期糖尿病等产科并发症、合并重要脏器功能障碍、妇科疾病及肿瘤；（2）试验药物禁忌或过敏；（3）椎管内麻醉禁忌证，如穿刺部位感染，凝血功能障碍等；（4）近半年有过试验相关药物使用史；（5）精神疾病史、慢性疼痛史；（6）晕动症，或术前有恶心、呕吐的患者；（7）因怀孕或其他疾病引起的瘙痒症状的患者。剔除标准：（1）腰硬联合麻醉效果不佳，麻醉平面高于 T_4 或低于 T_8，硬膜外置管不顺，硬膜外管回抽有血液或脑脊液等；（2）胎儿娩出后 5 min 内产妇有生命体征不稳、恶心呕吐、胸闷心悸、头晕头昏等症状。

1.2　分组　将符合研究条件的产妇，以随机数字表法，按剖宫产手术先后的顺序，将其分为艾司氯胺酮组和吗啡组，每组 50 例。两组产妇年龄、身体质量指数（body mass mdex，BMI）、产次等一般临床资料比较差异无统计学意义（$P>0.05$）。见表 1。艾司氯胺酮组：艾司氯胺酮 20 mg+罗哌卡因 9 mg+地塞米松 5 mg+生理盐水至 6 mL；吗啡组：吗啡 2 mg+罗哌卡因 9 mg+地塞米松 5 mg+生理盐水至 6 mL。

1.3　麻醉方法　所有参加试验的产妇在入手术室前均未使用术前用药，入手术室后，连接多功能监护仪，常规监测心电图、血压、心率、脉搏血氧饱和度，面罩吸氧，开放静脉通道快速滴入 300 mL 左右生理盐水

表 1　两组产妇一般临床资料比较　（$n=50$）

Tab. 1　Comparison of general clinical data between two groups　（$n=50$）

组别	年龄（岁，$\bar{x}\pm s$）	BMI［kg/m^2，$M(P_{25}, P_{75})$］	产次［$M(P_{25}, P_{75})$］
吗啡组	29.67±3.79	28.44(27.40,30.36)	2(1,2)
艾司氯胺酮组	30.62±4.87	28.90(28.04,30.72)	2(1,2)
t/Z 值	1.109	0.893	0.608
P 值	0.274	0.372	0.543

后,配合产妇摆好左侧胸膝卧位,定位 $L_{2\sim3}$ 椎间隙并标记,碘伏消毒,铺洞巾,于 $L_{2\sim3}$ 椎间隙穿刺进入硬膜外,经硬膜外针置入腰麻针,见脑脊液,接装有布比卡因的注射器回抽脑脊液稀释至 2.5 mL,再根据产妇的体重身高将 12~15 mg 布比卡因缓慢注入蛛网膜下腔,拔出腰麻针,经硬膜外针向头侧置入硬膜外导管,留管 3.5 cm,回抽无血液和脑脊液,固定好硬膜外导管后嘱产妇平卧,将手术床向左侧倾斜 20 度左右。5 min 后测椎管内麻醉的阻滞平面,测得阻滞平面在 T_6 水平左右,不高于 T_4 水平,不低于 T_8 水平。术中不经过静脉使用任何镇静镇痛剂,当产妇收缩压<90 mmHg 或血压下降超过基础血压 30%时,静脉注射盐酸麻黄碱注射液 6 mg 或者盐酸去氧肾上腺素注射液 100 μg 予以纠正,必要时重复;当心率<50 次/分,静脉注射硫酸阿托品注射液 0.25 mg,必要时重复。胎儿娩出 5 min 后,麻醉医生经硬膜外注入镇痛配方,术毕拔除硬膜外导管送回病房。术后产妇疼痛 VAS 评分超过 5 分,口服布洛芬胶囊 0.2 g 补救镇痛。

1.4　观察指标　主要指标:记录两组硬膜外给药后 5 min、术毕时、术后 24 h 和术后 48 h 产妇的 VAS 评分及两组术后补充镇痛药使用情况,记录两组硬膜外给药后 5 min 及术毕时产妇的 Ramsay 评分。次要指标:围术期两组产妇恶心呕吐、头晕头昏、幻视、噩梦、复视、大小便困难、皮肤瘙痒等不良反应。

1.5　统计学方法　经 PASS 11.0 的检验功效分析显示,在 5%的显著性水平下,本研究样本量对组间差异性检验功效达到了 100%。采用 SPSS 21.0 软件分析数据,计量资料先经 Kolmogorov-Smirnova 检验,如果符合正态分布,以 $\bar{x}\pm s$ 表示,比较采用独立样本 t 检验。不符合正态分布的计量数据以 $M(P_{25}, P_{75})$ 表示,比较采用 Mann-Whitney U 检验,重复测量资料的比较中,将其转换为正态分布数据后进行方差分析。计数资料用例(%)表示,组间比较采用 χ^2 检验。P<0.05 为差异有统计学意义。

2　结　果

2.1　不同时间点的 VAS 评分　两组产妇在硬膜外给药后 5 min、术毕时、术后 24 h 和术后 48 h 时 VAS 评分比较差异无统计学意义(P>0.05)。见表 2。

2.2　术后补充镇痛用药情况　两组术后首次使用补充镇痛药物的时间及人数占比差异无统计学意义(P>0.05)。见表 3。

2.3　Ramsay 评分　在硬膜外推药后 5 min 时,艾司氯胺酮组镇静评分显著高于吗啡组(P<0.05);术毕时,两组镇静评分差异无统计学意义(P>0.05)。见表 4。

2.4　不良反应情况　两组不良反应中恶心呕吐、头晕头昏、幻觉、噩梦、复视等发生率差异无统计学意义(P>0.05);吗啡组大小便困难及皮肤瘙痒发生率高于艾司氯胺酮组(P<0.05)。见表 5。

表 2　两组产妇 VAS 评分情况比较　[n=50, $M(P_{25}, P_{75})$]
Tab. 2　Comparison of the maternal VAS scores between two groups　[n=50, $M(P_{25}, P_{75})$]

组别	给药 5 min	术毕时	术后 24 h	术后 48 h
吗啡组	0(0,0)	0(0,0)	3(3,3)	1.5(1,2)
艾司氯胺酮组	0(0,0)	0(0,0)	3(3,4)	2(1,2)
$F_{组间}/P_{时间}$ 值	1473.294/<0.001			
$F_{组间}/P_{组间}$ 值	2.992/ 0.084			
$F_{交互}/P_{交互}$ 值	0.998/ 0.394			

表 3　术后两组产妇补充镇痛用药比较
Tab. 3　Comparison of postoperative supplementary analgesic medication between two groups

组别	用药占比[例(%)]	首次用药时间(h, $\bar{x}\pm s$)
吗啡组	6(12.00)	10.42±6.18
艾司氯胺酮组	5(10.00)	12.80±5.81
t/χ^2 值	0.653	0.102
P 值	0.530	0.749

表 4　两组产妇 Ramsay 评分比较　[n=50, $M(P_{25}, P_{75})$]
Tab. 4　Comparison of maternal Ramsay scores between two groups　[n=50, $M(P_{25}, P_{75})$]

组别	给药 5 min	术毕时
吗啡组	2(2,2)	2(2,2)
艾司氯胺酮组	2(2,3)	2(2,2)
Z 值	2.499	0.980
P 值	0.012	0.327

表 5　两组孕妇不良反应的发生情况　[n=50, 例(%)]
Tab. 5　Occurrence of adverse reactions in pregnant women in both groups　[n=50, 例(%)]

组别	恶心呕吐	头晕头昏	幻觉、噩梦、复视	大小便困难	皮肤瘙痒
艾司氯胺酮组	5(10.00)	9(18.00)	4(8.00)	2(4.00)	0
吗啡组	9(18.00)	6(12.00)	0	11(22.00)	9(18.00)
χ^2 值	1.329	0.706	2.344	7.162	7.814
P 值	0.249	0.401	0.126	0.007	0.005

3　讨　论

近年来瘢痕子宫和高龄产妇的比例增加,安全舒适的术后镇痛已成为人们普遍关注的问题[7]。本研究中的产妇选择的均是腰硬联合麻醉,已预先在硬膜外留置了硬膜外导管。单次硬膜外镇痛具有简单方便、费用低廉、可以更早下床活动、无需担心持续硬膜外留置导管带来的的感染、神经并发症、抗凝、导管打

折、脱管、呼吸抑制、影响早期下床活动等问题。本研究结果显示,单次硬膜外注射艾司氯胺酮可以提供良好的术中镇静和术后镇痛,其不良反应较少。

艾司氯胺酮在硬膜外的镇痛的机制可能是在这四个作用位点:(1) 艾司氯胺酮是中枢神经系统 NMDA 受体非特异性阻断剂,它产生全身麻醉、镇痛的主要机制是阻断兴奋性神经传导的 NMDA 受体。NMDA 受体主要分布在大脑和脊髓,硬膜外注射艾司氯胺酮后,通过弥散进入蛛网膜下腔,阻断脊髓 NMDA 受体的作用,经过脑脊液循环至颅内,作用于大脑 NMDA 受体;(2) 艾司氯胺酮与脑、脊髓内阿片受体结合,使阿片受体兴奋,艾司氯胺酮具有一定的阿片 μ 受体激动作用[8];(3) 艾司氯胺酮可通过阻滞电控性钠通道,对脊髓和周围神经具有显著的局部麻醉作用,但其局部麻醉作用较弱,大剂量使用全身麻醉会掩盖局部麻醉作用[9];(4) 艾司氯胺酮具有较强的抗炎作用,有研究指出艾司氯胺酮可以显著地降低炎症因子白细胞介素(interleukin, IL)-6 与 IL-8 水平,并升高抗炎症因子 IL-10 水平[10]。艾司氯胺酮已经被证实可以安全用于剖宫产手术麻醉[11],使用剂量与术后出现幻觉、噩梦、烦躁等精神状态发生率呈正相关,因此,使用阈下剂量成为一种理想的用药方案。既往有研究显示硬膜外注射 0.25 mg/kg 艾司氯胺酮联合局麻药可以取得更好的镇痛效果,该研究同时观察到椎管内使用艾司氯胺酮有补偿拟交感活性的作用,且没有全身作用[12]。

本研究中,硬膜外腔注射艾司氯胺酮具有类似吗啡的术后镇痛作用,但吗啡的作用时间更长,分析原因可能是由于艾司氯胺酮是亲脂性的,作用时间较短。硬膜外腔注射艾司氯胺酮在术中镇静效果更佳,是因为艾司氯胺酮具有高度脂溶性和低蛋白结合率的特点,很容易通过血脑屏障或经脑脊液进入脑,产生镇静效果[13]。而水溶性吗啡经硬膜外给药后,极少量透过血脑屏障或经脑脊液进入脑,产妇可一直保持配合和一定的定向力[14],本研究结果与之相符。另外,吗啡组产妇出现恶心、呕吐的发生率稍高于艾司氯胺酮组,而头晕头昏、幻觉、噩梦、幻视的不良反应,艾司氯胺酮组发生率比吗啡略高;两组术后大小便困难、瘙痒发生率差异有统计学意义,提示硬膜外注射艾司氯胺酮相比吗啡,用于术后镇痛有明显的优势。

国外关于艾司氯胺酮应用于硬膜外的报道较多,动物实验及临床试验证实,相对于静脉给药,相同剂量的艾司氯胺酮硬膜外给药可以取得更强镇痛效果[7]。艾司氯胺酮联合局部麻醉药用于椎管内,可以显著延长镇痛时间,改善镇痛评分,减少镇痛药物的使用[7]。Feltracco 等[15]研究纳入了 140 例行单肺切除术患者,在术中连续硬膜外输注给予亚麻醉剂量艾司氯胺酮,观察胸腔切开术后疼痛的镇痛作用,结果显示硬膜外输注亚麻醉剂量的艾司氯胺酮跟罗哌卡因相比,前者的术后镇痛效果更佳。王晖玥等[16]通过随机对照试验来探究阈下剂量艾司氯胺酮对老年髋关节置换术患者腰硬联合阻滞效果的影响,其指出硬膜外腔注射阈下剂量艾司氯胺酮可使患者麻醉后血流动力学保持相对稳定,明显延长镇痛时间,并降低术后疼痛评分,提高术后早期的镇痛效果,且未增加不良反应的发生率。

目前对艾司氯胺酮在硬膜外的研究仍很少,本研究发现艾司氯胺酮单次应用于硬膜外有良好的术后镇痛作用,术中镇静效果更佳,且副作用较少,但其作用确切机制仍不明确。在未来的研究中,笔者将针对上述存在的问题,加入客观指标,增加样本量,并继续探索硬膜外应用艾司氯胺酮的最佳剂量,为临床用药提供参考。

总之,艾司氯胺酮与吗啡单次硬膜外应用对剖宫产围术期均有良好的镇痛效果,且艾司氯胺酮单次硬膜外应用对剖宫产术中镇静效果及减少术后不良反应发生方面优于吗啡。硬膜外腔单次注射艾司氯胺酮是剖宫产镇痛的较好选择,特别对基层医院,具有简单、安全可靠、副作用少、费用低廉等优点。

利益冲突　无

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