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To evaluate the efficacy and safety of dezocine combined with lidocaine in local anesthesia for percutaneous testicular sperm aspiration

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Abstract: A total of 130 patients who underwent percutaneous testicular sperm aspiration from March 2021 to February 2023 were randomly divided into a Dezocine group and a control group. The Dezocine group received a muscle injection of 0.05mg/kg Dezocine 30 minutes before surgery, while the control group received a muscle injection of 0.01ml/kg normal saline. Both groups received 3ml of 2% lidocaine for spermatic cord block anesthesia. The anesthesia onset time, anesthesia duration, numeric rating scale (NRS) score, anesthesia satisfaction rate and incidence of adverse reactions were recorded and compared between the two groups. The statistical results showed that there were significant differences between the two groups in terms of anesthesia onset time, anesthesia duration, anesthesia satisfaction rate, non-steroidal anti-inflammatory drug (NSAID) use within 24 hours after surgery and NRS scores at 15 minutes, 1 hour and 2 hours after surgery. The incidence of adverse reactions in the Dezocine group was lower than that in the control group, but the difference was not statistically significant. The combination of Dezocine and lidocaine for spermatic cord block anesthesia during percutaneous testicular sperm aspiration is safe, effective and associated with fewer adverse reactions. It is suitable for clinical application and promotion in reproductive medicine outpatient surgery.

Keywords: Dezocine, lidocaine, local anesthesia, percutaneous testicular sperm aspiration.

INTRODUCTION

Surgical sperm extraction combined with intra-cytoplasmic sperm injection (ICSI) is the treatment of choice for couples with azoospermia-related infertility that cannot be treated conservatively. There is growing evidence that ICSI with testicular sperm rather than ejaculated sperm improves pregnancy rates (Esteves and Roque, 2019; Lopes and Esteves, 2019). The main types of surgical sperm extraction include percutaneous testicular sperm aspiration (TESA), conventional open testicular sperm aspiration (TESE), microsurgical testicular sperm aspiration (mTESE) and percutaneous epididymal sperm aspiration (PESA). Although the use of different testicular sperm extraction methods depends on the cause of the azoospermia and the skill of the surgeon, there is no general consensus as to which method is best for achieving higher SSR rates. Conventional open testicular sperm aspiration (TESE) tends to be used less frequently because of its high invasiveness and significant postoperative complications. Clinical studies have shown that embryo development and clinical outcomes are better in the TESA group than in the mTESA (microsperm extraction) group (Hu *et al*, 2021) and TESA is the preferred method of surgical sperm extraction in fertility centers (Lopes and Esteves, 2019). Percutaneous testicular sperm aspiration (TESA) is a surgical procedure that extracts sperm from the testicles and has become popular and widely used (Fertil Steril. 2019). The anesthetic methods used during this procedure vary widely and include general anesthesia, continuous epidural anesthesia (An *et al.*, 2018), spermatic cord anesthesia and local anesthesia (Pavan-Jukic *et al.*, 2020), with the choice of anesthetic method largely dependent on the experience and habits of the operator.

Surgical sperm extraction is a relatively simple surgical procedure and the traditional method of anesthesia is general anesthesia or spinal block with or without intravenous sedative drugs. However, if general anesthesia or spinal block is used, outpatients have to be converted to inpatient care; specialist anesthetic equipment, life support systems and specialist nursing staff are also required, which can greatly increase the financial burden on patients. Anesthetic and sedative drugs can also cause nausea and vomiting in patients. Some doctors also use local anesthetic methods, usually using infiltration anesthesia with a puncture channel in the operative area. However, testicular puncture involves repeatedly moving the puncture needle in and out of the testicle and the nerves innervating the testicle are visceral nerves that enter and exit mainly through the spermatic cord tissue, so anesthetic drugs do not always reach deep into the puncture channel. The analgesic effect of local anesthesia is inaccurate. The current conventional method of anesthesia uses spermatic block anesthesia and intravenous sedative drugs are not generally used. Percutaneous testicular aspiration for sperm extraction (TESA) is a relatively simple outpatient procedure (Zhu *et al.*, 2018). From an anatomical point of view, it is possible to provide effective anesthesia using spermatic

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cord block anesthesia alone. However, most patients express great concern about this method, most likely because the sperm extraction is performed on a very delicate part of the male body. For this and other reasons related to the high expectations of the procedure, patients undergoing the procedure may remain more anxious on the day of the procedure.

The commonly used anesthesia method is ipsilateral spermatic cord block, which allows for a smooth operation and is easy to perform, but it still has insufficient analgesic effect and some patients experience discomfort and pain in the testicles or lower abdomen. Comfort and anesthesia satisfaction are poor in some patients.

Dezocine is an effective analgesic that has partial agonist and antagonist activity of opioids and can effectively relieve moderate to severe pain (Ye, 2022). There have been reports in the literature of preoperative intramuscular Dezocine for preemptive analgesia (Zhou *et al.*, 2018). This study aims to explore the clinical efficacy and safety of Dezocine combined with lidocaine for spermatic cord block anesthesia during percutaneous testicular sperm aspiration.

MATERIALS AND METHODS

Study design and participants

130 patients who underwent percutaneous testicular sperm aspiration in our department from March 2021 to February 2023 were selected as the study subjects. Inclusion criteria: diagnosed with azoospermia and willing to undergo testicular sperm aspiration as a diagnosis or to provide sperm for ICSI; patients with anejaculation and erectile dysfunction who have a desire for fertility and ineffective drug treatment. Exclusion criteria: surgical contraindications, such as severe pulmonary and cardiac diseases, coagulation disorders, scrotal skin diseases, alcohol abuse, severe urinary tract infections and self-withdrawal from observation. Each patient received written informed consent. Based on a random, double-blind design and a control method, 130 patients who underwent percutaneous testicular sperm aspiration were included in this study. With the help of a computer-generated random number table, the subjects were randomly allocated into two groups: the Dezocine group (65 cases), which received intramuscular Dezocine 0.01ml/kg 30 minutes before surgery (5mg/1ml, Yangtze River Pharmaceutical Group Co., Ltd., National Drug Approval Number H20080329); and the control group (65 cases), which received intramuscular saline 0.01ml/kg 30 minutes before surgery. The volume of the medication was consistent. Local anesthesia was performed using conventional spermatic cord block anesthesia. The patients voluntarily participated in the study and signed the surgical informed consent form. The study was approved by the Ethics Committee of the First Affiliated Hospital of Gannan Medical University. The age range of the Dezocine group was 26-37 years old and the control group was 28-41 years old. Patient height was recorded and body mass index (BMI) was calculated. Testicular volume was measured using ultrasound.

Anesthesia method and surgical procedure

Before surgery, patients underwent relevant examinations, including electrocardiogram, prothrombin time and infectious disease-related tests and signed the surgical informed consent form. One week before surgery, patients should avoid using aspirin and other drugs, shave their scrotal hair the night before surgery and empty their bladder before entering the operating room. Thirty minutes before local anesthesia, a nurse who did not participate in the study injected Dezocine or an equal amount of saline into the patient's muscle based on a computer-generated random number sequence. The nurse did not reveal the type of injection to the patient throughout the process. Spermatic cord block anesthesia was performed using 2% lidocaine and the technique used was the injection of the vas deferens nerve block outside the spermatic cord (Li *et al.*, 1992). The specific steps were as follows: First, disinfect the area with povidone-iodine, from the middle of the abdomen to the upper thigh and then expose the scrotum with a surgical drape. Before injecting the anesthesia, touch and fix the vas deferens under the scrotal skin and use the three-finger method developed in China to separate the vas deferens from the internal blood vessels of the spermatic cord. Manipulate the vas deferens to the upper surface position below the midline with the middle finger and fix it with the index finger and thumb on the upper and lower sides of the scrotal midline. The injection point is above the vas deferens between the thumb and index finger. Use 2% plain lidocaine to raise a skin mound with a diameter of 1.5 cm in the dermis and subcutaneous tissue. Without injecting the anesthesia, insert the needle directly adjacent to the vas deferens and parallel to the outer ring of the inguinal canal. Before injecting lidocaine, gently aspirate the syringe to confirm that it has not pierced into the blood vessel and slowly inject 3ml of lidocaine. After the anesthesia is completed, fix the testicle with fingers, compress the scrotal skin by squeezing the testicle outward from the edge and slowly insert a 5-milliliter disposable syringe with a side-hole needle into the testicular parenchyma. After repeated aspiration 4-9 times, maintain negative pressure of the syringe and slowly withdraw it. Use the negative pressure of the syringe to aspirate the thread-like seminiferous tubule tissue. The seminiferous tubule tissue of the testis has some elasticity. The assistant pulls the exposed seminiferous tubule tissue with an ophthalmic forceps in a timely manner and after cutting the root of the exposed tissue, the testicular tissue and saline are discharged into multiple clean containers containing sperm preservation

solution and sent to the laboratory for testing, for ICSI or biopsy.

Questionnaires

After completion of lidocaine anesthesia, the assistant records the onset time of anesthesia, the number of punctures and the duration of surgery. Because the numerical rating scale (NRS) is relatively sensitive to adult language expression, NRS scoring is used to evaluate the analgesic effect (Parvizrad and Nikfar, 2022). Pain assessment is performed at 15 minutes, 1 hour, 2 hours, 6 hours, 12 hours and 24 hours after surgery, using the NRS (0-10 points): 0 points represent no pain and 10 points represent the maximum level of pain. Patient satisfaction with analgesia is scored as follows: 1 point for very satisfied, 2 points for satisfied and 3 points for dissatisfied. The patient's postoperative analgesic satisfaction is recorded 24 hours after surgery. The duration of anesthesia and postoperative adverse reactions are recorded. Adverse events are defined as symptoms such as dizziness, nausea, vomiting, cold sweats and hematoma that occur during the period. The amount of non-steroidal pain medication used by the patient within 24 hours after surgery is recorded and the same medication, sodium diclofenac enteric-coated tablets (25mg/tablet, drug registration standard JX20160303), is used. It is generally taken as needed and no more than 6 tablets are taken within 24 hours.

Ethical approval

The clinical trial procedure was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Gannan Medical College with written approval, and the experiment was conducted in accordance with its guidelines (LLSC-2023-180).

STATISTICAL ANALYSIS

This passage describes the use of descriptive statistical methods to analyze observational data. Normally distributed data is presented using mean±standard deviation, while nonparametric data is presented using median (25%, 75%). Age, BMI and volume of the affected testicle are analyzed using an independent sample t-test based on normally distributed data. Height, NRS and other data are analyzed using nonparametric Mann-Whitney U statistical methods. Comfort level 24 hours after surgery and postoperative pain satisfaction are observed using a chi-square test and the incidence of adverse events is determined using Fisher's exact test ($n<5$). A p-value less than 0.05 is considered to indicate a statistically significant difference. All analyses were performed using SPSS26.0.

RESULTS

Demographic information

Two groups of patients were compared in terms of age, height, body mass index, prothrombin time and testicular size (table 1) and there were no statistically significant differences in demographic data between the two groups. The two groups of studies were comparable.

Onset and duration of anesthesia

The time elapsed between the onset of lidocaine injection and the end of pain-free skin clamping by toothless forceps was recorded as the onset of anesthesia. As shown in fig. 1(A), The onset of anesthesia was found to be significantly lower in the Dezocine group (5.02±1.10 minutes) than in the saline control group (10.0±2.03 minutes), with a significant difference (t=-17.55, p=0.000). Fig. 1 (B) shows the duration of anesthesia in both groups, the difference between the two groups was significant in the Dezocine group (2.73±0.45(h)) control group (2.61±0.32(h)) (t=1.710 P=0.009)

Anesthetic effect (NRS score) and anesthetic satisfaction score

Postoperative NRS scores were performed at 15min, 1h, 2h and 6h, 12h and 24h postoperative time slots. The results are shown in fig. 2. The NRS scores (C) were significantly lower in the Dezocine group than in the control group at 15 min (z=-4.507 P=0.000), 1h (z=-2.367 P=0.018) and 2h (z=-2.352 P=0.019) postoperatively, with a significant difference; The differences in NRS scores were not significant at 6h (z=-0.625 P=0.567), 12h(z=-0.869 P=0.385）and 24h (z=-1.150 P=0.250). Fig. 2(D) shows the statistical results of postoperative anesthetic satisfaction. The Dezocine group was very satisfied (36, 9%), satisfied (44, 6%) and dissatisfied (18.5%); the control group was very satisfied (21.5%), satisfied (38.5%) and dissatisfied (40%).There was a statistically significant difference in anesthetic satisfaction between the two groups (z=8.086 p=0.018), with higher satisfaction with anesthesia in the Dezocine group than in the control group. Preoperative NRS scores and anesthetic satisfaction scores were consistent between the two groups.

Comparison of the incidence of adverse reactions and the amount of NSAIDs used in the 24h postoperative period

The statistical results in fig. 3 (E) show the amount of non-steroidal analgesics used within 24 hours after surgery. The amount used in the Dezocine group was 3 (1, 4), which was statistically significantly lower than the control group's 3 (2, 4) (z=-2.081, P=0.03).

Patients in the Dezocine group required less analgesic medication for pain relief within 24 hours after surgery. Fig. 3 (F) shows the incidence of postoperative adverse reactions.

For comparison purposes, patient occurrences during the perioperative period were defined as adverse events and accumulated. There were 63 cases (96.92%) with no

Table 1: General conditions of patients in the dezocine and control groups

Parameters	Dezocine Group	Control Group	Z-value (t)	*P-value*
Age (years)	33.0±4.1	33.4±3.3	-4.87	0.112
Height (m)	152-174	148-177	-1.159	0.247
BMI	19.3±4.4	21.7±4.2	-3.220	0.966
Prothrombin time (min)	7.4-10.7	7.7-11.3	-1.326	0.185
Testicular volume on the operated side (ml)	11.7±2.7	14.6±2.8	-6.170	0.835

Values are the mean ± S.D, Prothrombin time is not normally distributed. BMI:body mass index.

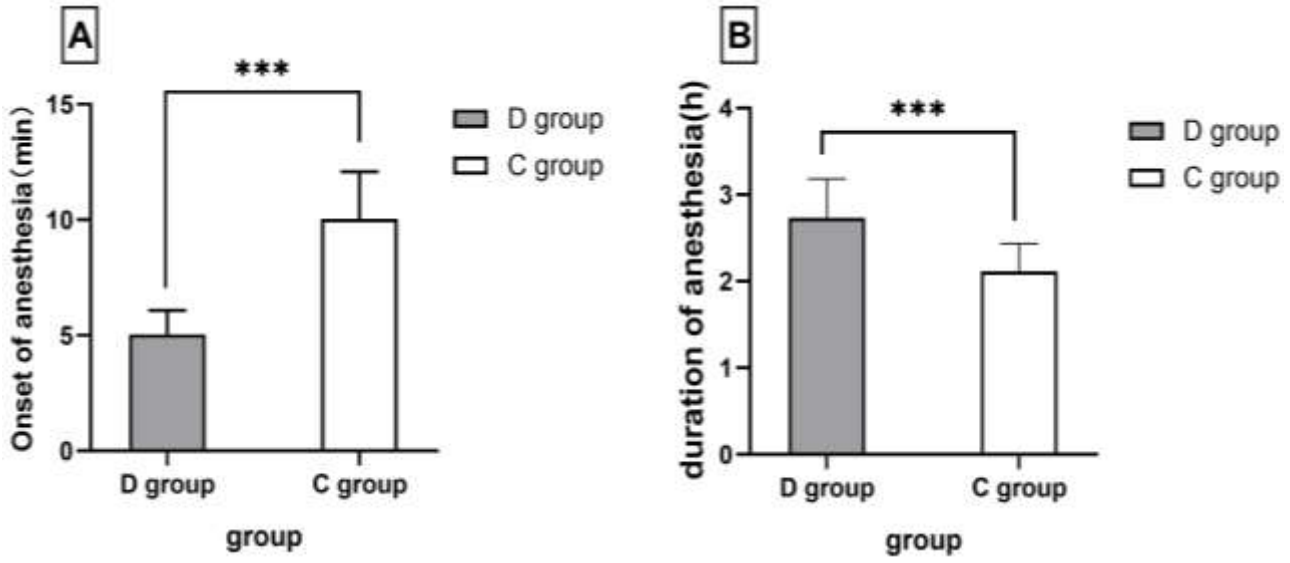

Fig 1 A & B: Onset of anesthesia and duration of anesthesia

As shown in fig. 1 (A) the onset of anesthesia in the dezocine group was significantly lower than that in the saline control group and the difference was significantly significant. As shown in fig. 1 (B) showing the duration of anesthesia in both groups, the duration of anesthesia in the dezocine group was longer than that in the control group, and the difference between the two groups was significant. ***:p<0.001

adverse reactions in the Dezocine group and 2 cases (3.08%) with adverse reactions. In the control group, there were 6 cases (9.23%) with adverse reactions and 59 (90.77%) with no adverse reactions. There was no statistically significant difference between the two groups (P=0.2735).

DISCUSSION

Testicular epididymal sperm aspiration (TESA) is a surgical method of inserting a needle percutaneously into the testis and using negative pressure to extract the contents of the seminiferous tubules for pathological examination or ICSI. Currently, there are few studies describing the anesthesia technique for testicular sperm retrieval and there is a wide variation in the type of anesthesia used during the procedure, which is also related to the experience and habits of the surgeon. Different types of anesthesia have their advantages and disadvantages (Cito *et al.*, 2019).

Some scholars choose spinal anesthesia or general anesthesia, which significantly increases the cost of treatment for patients. TESA outpatient surgery can be performed under local anesthesia and patients usually leave the hospital within a few hours after the procedure. However, if general anesthesia or spinal anesthesia is used, patients generally need to gradually recover normal activity on the second day after the procedure. General anesthesia or sedative drugs may cause a high incidence of postoperative nausea and vomiting (Alizadeh and Fard, 2019; Belrose and Noppens, 2019) and these symptoms make patients even more afraid than the postoperative pain itself (Weibel *et al.*, 2021). In addition, the risks of general anesthesia, the need for professional equipment and personnel to monitor postoperative vital signs and other factors need to be considered. Spermatic cord block anesthesia is a common and widely used anesthesia method for testicular, epididymal and vas deferens surgery. However, spermatic cord block anesthesia not only has the risk of postoperative skin bruising and spermatic cord hematoma, but also has the risks of incomplete anesthesia or the need for repeated blockade, vagal nerve reactions, puncture of surrounding tissues including vas deferens and other risks (Mulhall and Jenkins, 2017). Moreover, because the testis and scrotal

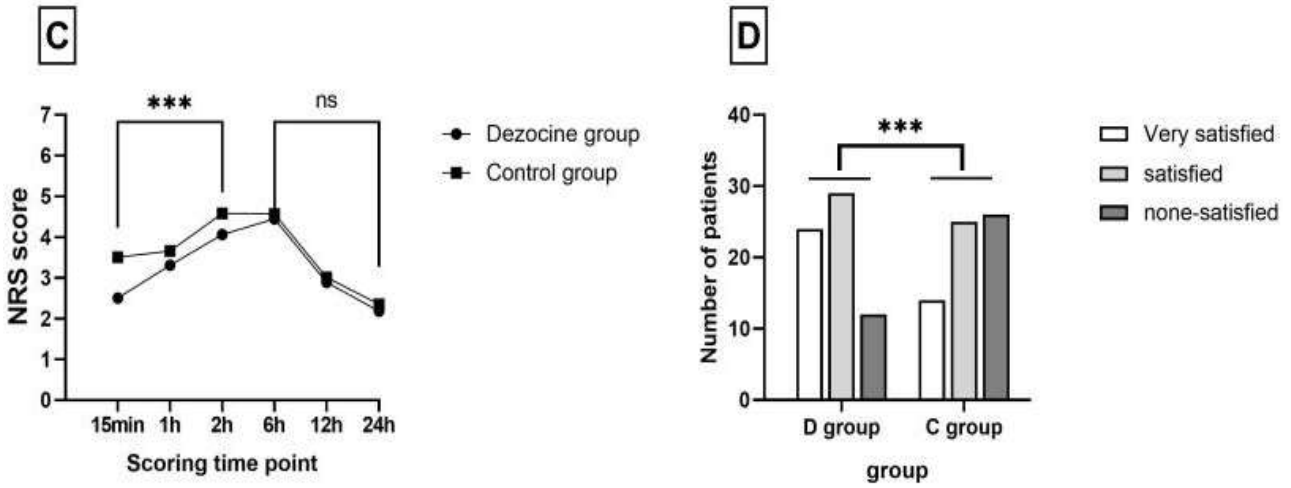

Fig. 2 C & D: Anesthetic effect (NRS score) and anesthetic satisfaction score

As shown in fig. 2(C), the differences in postoperative NRS scores were different between the two groups at different postoperative time periods. In the postoperative 15min, 1h and 2h postoperative time periods, the NRS scores in the dezocine group were significantly lower than those in the control group, and the differences were significant, **:$p<0.001$; the differences in the NRS scores at 6h, 12h and 24h were not significant. ns: $p>0.05$. As shown in fig. 2(D), anesthesia satisfaction was higher in the dezocine group than in the control group. Comprehensive C and D statistical data found that perioperative NRS scores and anesthesia satisfaction scores were consistent in the comparison between the two groups. ***:$p<0.001$

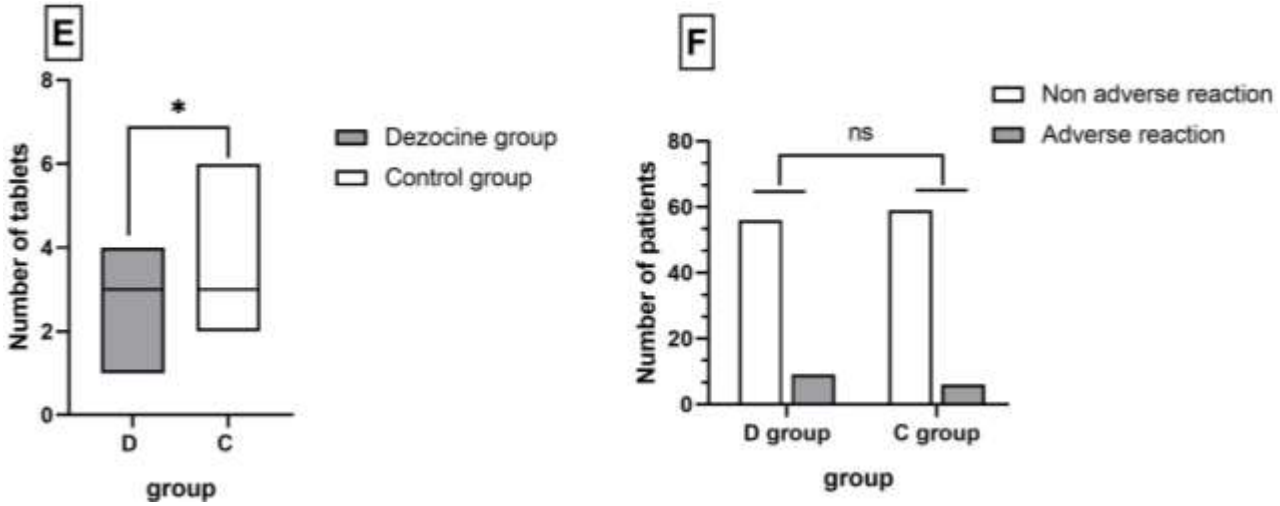

Fig. 3 E & F: As shows the amount of NSAIDs used in the 24h postoperative period and the incidence of postoperative adverse effects.

As shown in Fig. 3 (E) less pain medication was required for pain relief in patients in the dezocine group in the 24h postoperative period. * $p<0.05$.There was no statistically significant difference between the two groups when comparing the incidence of adverse reactions in the dezocine group and the control group as shown in fig. 3(F). ns:$p>0.05$.

skin are innervated by different nerves (Fahmy, 2022), incomplete blockade often occurs in clinical practice. Spermatic cord block anesthesia is not a perfect anesthesia method.

TESA involves sensitive organs in the male testis and the surgical steps require repeated punctures of the testis at multiple points. During the procedure, patients still experience varying degrees of discomfort and pain in the surgical area and their comfort and anesthesia satisfaction are poor (Verza and Esteves, 2019). In order to reduce postoperative complications and improve patient anesthesia satisfaction, this study explores the effectiveness and safety of the combined use of dezocine and lidocaine in local anesthesia for testicular sperm retrieval via percutaneous testicular puncture.

Dezocine is becoming the leading drug in the Chinese market for the relief of moderate to severe pain. It is believed that the clinical efficacy of dezocine and the chance of causing adverse effects during treatment are minimal. This is mainly attributed to its partial agonist activity on mu-opioid receptors and the preferential binding of Dezocine to mu-opioid receptors over κ and δ

opioid receptors; also, Dezocine shows a limited sedative effect with an upper limit of moderate effects. At moderate doses, the upper limit of the sedative effect was reached (Wang *et al.*, 2018).There are many research articles on dezocine used in the perioperative period in China and most of the studies focus on its effects on patients undergoing general anesthesia and epidural anesthesia. There are few studies on the effects of dezocine on perioperative pain management in patients receiving local anesthesia (Zhao *et al.*, 2022). Currently, there are no reports on the use of dezocine in local anesthesia for reproductive system surgery. The routes of dezocine administration include intravenous infusion, intramuscular/subcutaneous injection and others. The elimination half-life after intravenous injection is approximately 2.6-2.8 hours and is independent of the dose. The onset time after subcutaneous or intramuscular injection is only half an hour, making it suitable for outpatient surgery (Liu *et al.*, 2018). Therefore, this study used intramuscular injection of dezocine 30 minutes before surgery.

As shown in figs. 1 and 2, this study indicates that the combination of intramuscular injection of Dezocine and lidocaine for local anesthesia before surgery significantly shortens the onset time compared to the use of lidocaine alone, demonstrating the good analgesic effect of Dezocine. It also prolongs the duration of anesthesia, which is theoretically consistent with the longer half-life of dezocine.

Because the pain rating scale is highly sensitive, the NRS rating mechanism was used as the anesthesia evaluation tool. The surgery usually takes about 30-60 minutes, so the rating time points were chosen at 15 minutes, 1 hour, 2 hours, 6 hours, 12 hours and 24 hours after surgery. The results of the study (fig. 3) show that the NRS ratings of the dezocine group were significantly lower than those of the control group from 15 minutes to 1 hour after surgery, with statistically significant differences in the ratings. From 6 hours after surgery, the NRS ratings of the two groups gradually approached each other and the rating differences lost statistical significance, which may be related to the gradual decrease in drug concentration after the peak of the half-life of dezocine. Fig. 4 shows that the patient satisfaction with anesthesia in the dezocine group was significantly higher than that in the control group, which is consistent with the NRS rating results. This study demonstrates that the application of dezocine in local anesthesia for testicular sperm retrieval via percutaneous testicular puncture is significantly effective.

It is interesting that the clinical application of dezocine began in Western countries in the 1980s, but currently it is less commonly used clinically in Western countries while it is more popular in China. In 1980, researchers used a dose of 20mg Dezocine for pain relief via intramuscular injection in patients with urogenital pain, which had a very good effect but also caused obvious nausea and vomiting symptoms (Oosterlinck and Verbaeys, 1980). More clinical applications later found that intramuscular Dezocine had side effects such as nausea and vomiting, although rare, which may be related to the dosage (Wang *et al.*, 2022). Later, a dose of 0.15mg/kg was commonly used clinically, which had a significant analgesic effect and a maximum dose of 0.3mg/kg had a ceiling effect on analgesia (Zhou *et al.*, 2018). In 2021, Chinese researchers reported the use of a dose of 0.05mg/kg (Feng *et al.*, 2021), which had a high safety and low incidence of adverse reactions. Therefore, this study used a dose of 0.05mg/kg and the total amount of non-steroidal analgesics used within 24 hours after surgery showed a statistically significant difference between the two groups, with the Dezocine group requiring less analgesics within 24 hours after surgery, as shown in figs. 5 and 6. Literature reports that Dezocine has few adverse reactions or even no adverse reactions when used for local anesthesia. Although this study suggested that the Dezocine group had significantly fewer adverse reactions than the control group, there was no statistically significant difference between the two groups. The reason for this may be due to the involvement of sensitive and special areas of male pain in the surgical scope, as well as a small sample size.

Currently, the specific mechanism by which opioid drugs enhance the effect of local anesthetics is not clear. Studies have shown that there are also opioid receptors on the surface of peripheral nerves and local application of exogenous opioid agonists can produce analgesic effects by activating peripheral opioid receptors in the tissue, without activating central nervous system opioid receptors, thus the incidence of side effects mediated by central opioid receptors, such as sedation, respiratory depression, confusion, or addiction, is extremely low (He, 2020). In summary, this project showed that preoperative intramuscular Dezocine for percutaneous testicular sperm aspiration and spermatic cord block anesthesia is effective and safe.

However, this study also has limitations. As a clinical study, the research project did not involve the impact of the drug on sperm. Human sperm has K and μ opioid receptors and continuous exposure of human sperm to different opioid drugs *in vitro* can cause varying degrees of inhibition of sperm (Seeber *et al.*, 2019). Dezocine only has inhibitory effects at high concentrations and does not affect sperm vitality at low concentrations. Currently, there is a lack of *in vivo* experiments on the effect of Dezocine on male sperm and the evidence for its safety is weak (Xu *et al.*, 2013). The sample size in this study was relatively small and increasing the number of cases may be needed to make the conclusions on the effectiveness and safety of dezocine in local anesthesia for reproductive system surgery more convincing.

CONCLUSION

The use of Dezocine combined with lidocaine for local anesthesia during percutaneous testicular aspiration is effective, safe and provides a new option for TESA surgical anesthesia suitable for promotion in clinical work in outpatient reproductive surgery.

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