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ARTICLE

Clinical Research

Efficacy and safety of periprostatic nerve block combined with perineal subcutaneous anaesthesia and intrarectal lidocaine gel in transrectal ultrasound guided transperineal prostate biopsy: A Prospective Randomised Controlled Trial

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Abstract

Background To determine the efficacy and safety of a periprostatic nerve block combined with perineum subcutaneous anaesthesia and intrarectal lidocaine gel for transrectal ultrasound-guided transperineal prostate biopsy (TPBx) through a prospective randomised controlled trial.

Methods In total, 216 patients from May 2018 to November 2018 were randomly assigned to the experimental group and the control group at a ratio of 1:1. The experimental group received a periprostatic nerve block combined with subcutaneous perineal anaesthesia and intrarectal lidocaine gel. The control group received total intravenous anaesthesia. A visual analogue scale (VAS) score (0–10) was used to evaluate pain at different stages. The operative time, duration of hospitalisation, intraoperative vital signs, perioperative complications and clinicopathological features were recorded.

Results The overall detection rate of prostate cancer was 40.74%, and the median Gleason score was 8 for all patients diagnosed with prostate cancer. No significant differences in terms of detection rates, Gleason scores and ISUP/WHO Grade Groups were found between the two groups ($P > 0.05$). The experimental group had no pain or just met the criteria for mild pain during the biopsy, which was significantly alleviated after the biopsy, and had a shorter operation time compared with that of the control group ($P < 0.05$). Compared with the control group, the experimental group had more stable haemodynamics and respiratory status and fewer surgical complications ($P < 0.05$).

Conclusions In multiple aspects, a periprostatic nerve block combined with subcutaneous perineal anaesthesia and intrarectal lidocaine gel is a safer and more efficient approach to local anaesthesia for TPBx that can almost replace total intravenous anaesthesia and is worthwhile applying in the clinical setting.

Introduction

Prostate cancer (PCa) is the second most common cancer and fifth leading cause of cancer-related death in men worldwide [1]. The incidence of PCa has been increasing in both developed and developing countries and is likely to increase further in the coming decades [2]. Therefore, it is necessary to constantly improve the techniques for the early detection of PCa worldwide.

Transrectal ultrasound (TRUS)-guided transrectal prostate biopsy (TRBx) is a widely used technique for the diagnosis of PCa [3]. However, a prospective multicentre study showed that 5.2% of men experience infective complications after TRBx despite antibiotic prophylaxis, which could lead to resistance to antimicrobials and increased hospital admission rates [4, 5]. In addition, because TRBx cannot effectively acquire the anterior and apical regions of the prostate, false negatives often occur, which seriously affect the timeliness of diagnosis and treatment. This phenomenon is called Prostate Evasive Anterior Tumor Syndrome (PEATS) [6, 7]. In contrast, a series of published studies indicated that TRUS-guided

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transperineal prostate biopsy (TPBx) results in not only a rate of infective complications close to zero but also an elevated detection rate of PCa in the apex and anterior zone of the prostate [8–11].

During the TPBx procedure, the needle punctures the perineal skin and pelvic floor muscles, which are richly innervated by sensory branches of the pudendal nerve [8]. In contrast to TRBx, in which the needle passes through the rectal mucosa, TPBx causes severe pain unless the quality of the anaesthesia is excellent. Therefore, general anaesthesia has often been used for TPBx for better pain management. In recent years, some urologists have proposed the use of local anaesthetic methods for TPBx, which could also lead to the achievement of satisfactory biopsies [12–14]. A number of local anaesthesia methods reported in the literature have been tried in our hospital, but the advantages and disadvantages were mixed. Finally, we established a complete local anaesthesia process, which has been practised for more than 1 year and achieved good clinical effect in our hospital.

The aim of this study was to determine the efficacy and safety of this local anaesthesia technique for patients undergoing TPBx and to provide medical evidence through a prospective randomised controlled trial to promote its application in the clinical setting.

Patients and methods

Trial design and patient cohort

This study was approved by the Institutional Ethics Committee of Xiangya Hospital, Central South University and has been registered in the Chinese clinical trial registry (ChiCTR1800015999), which is the first-level registration authority of the World Health Organization International Clinical Trial Registration Platform. In total, 216 patients who underwent TPBx from May 2018 to November 2018 were enroled in this study in our hospital, and all of them signed informed consent forms. The experimental group received a periprostatic nerve block combined with subcutaneous perineal anaesthesia and intrarectal lidocaine gel. The control group received total intravenous anaesthesia.

Randomisation

All patients were randomly assigned to the control group or the experimental group at a ratio of 1:1. The randomisation was implemented with SPSS 19.0 for Windows, which randomly generated a series of numbers. The randomisation was conducted by an independent doctor to ensure that membership in each group could not be predicted (Fig. 1).

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) Prostatic nodules detected by digital rectal examination (DRE) with any level of prostate-specific antigen (PSA); (2) hypoechoic prostate nodules revealed by ultrasonography or/and abnormal signals revealed by MRI, with any level of PSA; (3) PSA >10 ng/ml, any levels of f/t PSA and prostate-specific antigen density (PSAD); and (4) PSA 4-10 ng/ml, but abnormal values of f/t PSA and PSAD. The exclusion criteria were as follows: (1) acute infection period or stage of fervescence with a temperature higher than 38 °C and other influenza-like symptoms; (2) hypertensive crisis, defined as severely elevated blood pressure (equal to or greater than 180 systolic or 120 diastolic); (3) decompensated heart failure, indicated by symptoms of heart failure including shortness of breath and tiredness; (4) some diseases with severe bleeding tendency, such as thrombocytopenia, leukaemia, allergic purpura or long-term use of antiplatelet drugs; (5) fluctuating blood glucose levels due to diabetes; glycosylated haemoglobin >8.5%; fasting blood glucose >10 mmol/L; random blood glucose >12 mmol/L; hypoglycaemic episodes, diabetic ketoacidosis or diabetic nonketotic hyperosmolar syndrome in the past 6 months; and (6) internal and external haemorrhoids, perianal lesions or rectal lesions.

Anaesthetic interventions

The experimental group: After completely exposing the perineal area, 5 ml of 2%-lidocaine and 1:200,000 adrenaline was injected into the anal ring and perineal skin to complete the subcutaneous perineal anaesthesia (Fig. 2a). Then, the TRUS probe coated with liquid paraffin and lidocaine gel was gently inserted into the rectum. We could observe the anatomy of the pelvic floor and prostate clearly on the ultrasonic image in real time. Denonvilliers' space was identified by the presence of hyperechoic fatty tissue between the rectum and prostate. Successful deep periprostatic anaesthesia after injection of local anaesthetics under ultrasonic visualisation was indicated by the hypoechoic expansion of Denonvilliers' space (Movie 1). Local anaesthesia was performed on both the right and left sides of the prostate. As shown in Movie 1, the drugs were injected in the right side first. The same procedure was performed on the other side of the prostate (Fig. 2b, c). Five minutes after the completion of the anaesthesia, the biopsy was initiated.

The control group: The patients were induced with fentanyl at a dose of 1 μg/kg, followed by 1.0 mg/kg propofol administered intravenously, and the biopsy was performed when the patient's eyelash reflex had disappeared. The maintenance of anaesthesia depended on the administration of propofol at a rate of 6 mg/(kg·h). All patients received

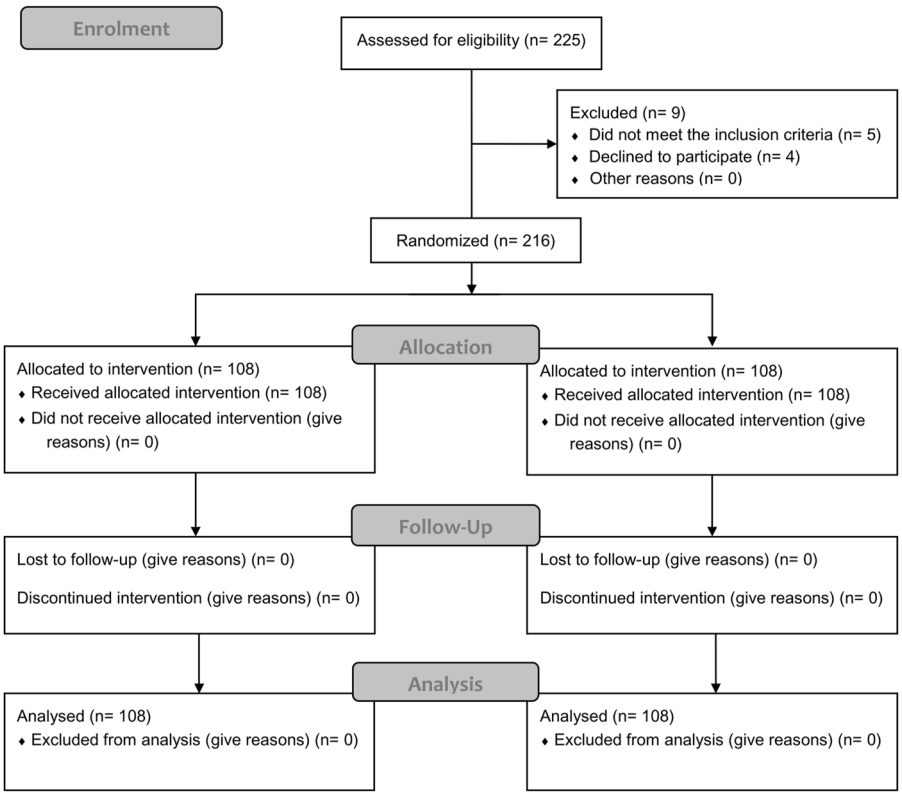

Fig. 1 Consort diagram of patient enrolment

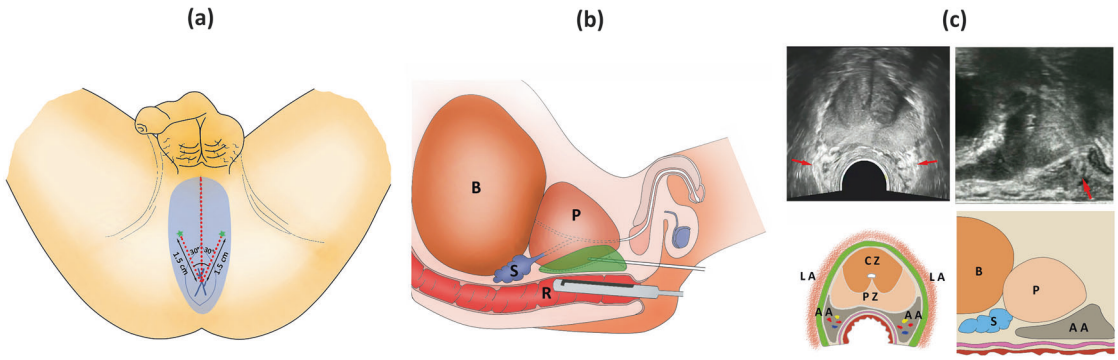

Fig. 2 Diagrams of perineal subcutaneous anaesthesia and periprostatic nerve block. **a** Area in blue shows the scope of subcutaneous anaesthesia; the green marks on both sides show the needle insertion points for periprostatic anaesthesia. **b** The green area indicates the anaesthetic injection site for periprostatic anaesthesia. B, bladder; P, prostate; S, seminal vesicle; R, rectum. **c** The prostate on the transversal and sagittal planes after the injection of anaesthetic. The red arrows represent the range of the anaesthesia drugs. P, prostate; CZ, the central zone of the prostate; PZ, the peripheral zone of the prostate; LA, levator ani; AA, the area of anaesthetic infiltration

oxygen via face mask inhalation at a rate of 6 L/min throughout the entire puncture process. If the patient showed signs of incomplete anaesthesia such as body movement during the puncture, an additional dose of propofol 0.4 mg/kg was administered. If the patient's blood pressure dropped more than 20% of the baseline value, the patient was given ephedrine (~6 mg each time). If the patient's heart rate (HR) was fewer than 60 beats per minute, the patient was given atropine 0.2–0.5 mg. If respiratory depression was observed in a patient (SpO_2 <92% as a standard), manual ventilation would be administered through the mask.

Surgical procedure

All patients on a low-residue diet were treated with sodium phosphate oral solution to prepare the bowel at 7 pm 1 day before surgery. The biopsy was performed with ultrasound

equipment (model: HI VISION Avius, Hitachi, Japan) combined with a TRUS probe (model: EUP-U533, Hitachi, Japan) and a one-time semiautomatic biopsy needle (model: MC1825, Bard, America). A transperineal stepper with a brachytherapy-like grid was connected to the probe, allowing transperineal access. The entire puncture process was performed by the same urologist with the assistance of an ultrasound technician. After the patient entered the operating room, peripheral venous access was established. The mean arterial pressure (MAP), HR, respiratory rate (RR) and SpO_2 were recorded before anaesthesia (T0), during anaesthesia (T1), during biopsy (T2) and 30 min after biopsy (T3). The patient was placed in the lithotomy position for the transperineal "12-core plus X" prostate biopsy protocol. The previously described systematic collection of 12 cores from six different sites was performed as follows: [15] anterior lateral (AL), posterior lateral (PL), anterior 1 (A1) and anterior 2 (A2) from the anterior parasagittal zone, posterior 1 (P1) and posterior 2 (P2) from the posterior parasagittal zone (Fig. S1). All the patients underwent pre-biopsy MRI. The operator reviewed the MRI images and correlated the suspicious areas with those viewed on the real-time TRUS images to guide additional targeted biopsies ("plus X") (cognitive fusion biopsy). All the biopsy specimens were placed individually in tubes containing 4% formalin.

Outcomes

The primary outcome

The primary outcome evaluated was the patient-reported degree of pain. Visual analogue scale (VAS) scores were used to assess the degree of pain, with 0 indicating no pain and 10 indicating unbearable pain [16]. Patients postoperatively completed a VAS questionnaire to describe the degree of pain experienced during anaesthesia (VAS1), during biopsy (VAS2), 6 h after the biopsy (VAS3) and 1 day after the biopsy (VAS4).

The secondary outcomes

The secondary outcomes included changes in vital signs during the procedure, the operative time, the volume of blood loss, the duration of hospitalisation and the incidence of postoperative complications. The operative time was the combined anaesthetic time and puncture time. The postoperative complications were infection, perineal haematoma, urethral bleeding, haematospermia, retention of urine and dysuresia.

All the observed indexes mentioned above were recorded by an independent urologist.

Sample size calculation

A priori sample size estimation was performed based on estimations of group means and standard deviations (SD). A difference of 0.5 points between the 2 groups' VAS scores was deemed to be clinically significant. To achieve this significance with an α level of 0.05 and a power (1-β) of 0.95, the estimated sample size was 105 patients in each group, with a 1:1 ratio.

Statistical analysis

The continuous variables that met the criteria for a normal distribution and homogeneity of variance were analysed by the independent sample *t*-test; otherwise, the Wilcoxon rank-sum test was used. The categorical variables were compared with the χ^2 test. In addition, two-factor repeated measure ANOVA was used to evaluate the differences in the repeated measures data. If the difference was significant, independent sample *t*-tests were used to determine the inter-group differences at different time points, and paired-sample *t*-tests were used to determine the intra-group differences between the value at each time point and the baseline value. The measurement data were presented as the means ± SDs. SPSS 19.0 was used for the statistical analysis. $P < 0.05$ was considered to indicate a significant difference. The data analysis was performed by an independent data analyst.

Results

There were no statistically significant differences between the two groups in terms of age, weight, height, prostatic volume, PSA, DRE findings, imaging (ultrasound, CT or MRI) findings and family history of PCa ($P > 0.05$). No significant difference in detection rates was found ($P = 0.782$). The overall detection rate of PCa was 40.74%, and the median Gleason score was 8 for all patients diagnosed with PCa. The Gleason scores and ISUP/WHO Grade Groups of the detected cancers did not significantly differ between the study arms (Table 1). Patients diagnosed with PCa had the following characteristics: high PSA values, high Gleason scores and late clinical stages (Fig. S2). Men with high-risk PCa accounted for the majority of all patients diagnosed with PCa (Fig. S2).

The analysis of efficacy included pain management, operative time and hospitalisation duration

In terms of pain control, the patients in the experimental group felt slight pain, while the control group reported almost no pain on VAS1 and VAS2. However, there were no

Table 1 Basic characteristics of the patients and biopsy results

	Control group	Experimental group	*P*-value
No. of patients	108	108	–
Age (years)	67.06 ± 7.55	66.50 ± 9.48	0.939
Weight (kg)	62.95 ± 9.79	63.90 ± 10.23	0.489
Height (cm)	166.73 ± 6.65	167.55 ± 6.56	0.366
Prostatic volume (ml)	54.00 ± 19.04	53.05 ± 15.43	0.907
PSA (ng/ML)	22.97 ± 24.78	22.00 ± 22.59	0.674
DRE findings (*n*, %)	81, 75.00%	90, 83.33%	0.132
Imaging findings (*n*, %)	102, 94.44%	105, 97.22%	0.496
Family history of PCa (*n*, %)	1, 0.93%	4, 3.70%	0.365
Positive detectable rate (*n*, %)	43, 39.81%	45, 41.67%	0.782
Gleason score (*n*, %)			0.332
Gleason 6	5, 11.63%	7, 15.56%	
Gleason 7	10, 23.26%	14, 31.11%	
Gleason 8	12, 27.91%	10, 22.22%	
Gleason 9	12, 27.91%	11, 24.44%	
Gleason 10	4, 9.30%	3, 6.67%	
ISUP/WHO Grade Group (*n*, %)			0.284
Grade Group 1	5, 11.63%	7, 15.56%	
Grade Group 2	3, 6.98%	6, 13.33%	
Grade Group 3	7, 16.28%	8, 17.78%	
Grade Group 4	12, 27.91%	10, 22.22%	
Grade Group 5	16, 37.21%	14, 31.11%	

significant differences in the pain reported on VAS3 and VAS4 between the two groups ($P > 0.05$; Table 2). With regard to the operative time, the experimental group needed a significantly shorter anaesthetic time ($P < 0.001$) but a slightly longer biopsy time when compared with those of the control group ($P < 0.001$). For the entire operation process (from entering the operating room to leaving the operating room), compared with the control group, the experimental group needed a significantly shorter time ($P < 0.001$; Table S1). There was no significant difference between the two groups in the hospitalisation duration ($P > 0.05$), and the average length of stay per patient was ~1 day (Table S3).

The analysis of safety included the steadiness of vital signs and occurrence of perioperative complications

With regard to the changes in the vital signs during the biopsy procedures, repeated-measures ANOVA revealed highly significant interblock variability, time dissimilarity and interaction of interblock variability with time dissimilarity ($P < 0.001$). Through further detailed analysis, we found that compared with the baseline values, the MAPs, HRs and RRs of patients in the experimental group increased slightly (MAP/ HR/ RR: $P < 0.001$), while the MAPs, HRs, RRs and SpO_2 values decreased significantly in the control group, especially at T2 (MAP/ HR/ RR/ SpO2: $P < 0.001$) (Table S2 and Fig. 3). Low MAP, low HR and respiratory depression were more likely to occur in the control group than in the experimental group. No significant differences were found in the incidence rates of complications, including infection, perineal haematoma, urethral bleeding, haematospermia, retention of urine and dysuresia ($P > 0.05$; Table S3).

Table 2 VAS scores during the perioperative period

Groups	VAS scores			
	VAS1	VAS2	VAS3	VAS4
Control group ($n = 108$)	0.00 ± 0.00	0.00 ± 0.00	1.06 ± 0.76	0.91 ± 0.78
Experimental group ($n = 108$)	2.92 ± 0.96	2.91 ± 1.09	1.03 ± 0.76	1.04 ± 0.82
P-value	NC	NC	0.810	0.238

NC not calculated

Discussion

TPBx has interested urologists in recent years [17]. However, it usually involves general anaesthesia in most medical institutes because it is more painful. The lack of an optimal local anaesthesia approach is the major obstacle to performing this procedure in outpatient clinics. We have performed TPBx with local anaesthesia in our hospital for over 1.5 years. This randomised controlled trial provided evidence for the safe and efficient application of local anaesthesia instead of general anaesthesia for transperineal prostate biopsies.

The cancer detection rate in the patient cohort in this study was 40.74%, which was not lower than that previously reported using both the transrectal and transperineal approaches [18, 19]. Therefore, we suggest that TPBx is an adequate method in terms of cancer detection.

This study adds to the literature on patient-reported degree of pain following transperineal prostate biopsy. In our study, although our local anaesthetic technique did not achieve completely painless effects, the VAS scores of the experimental group only averaged 2.92 ± 0.96 during anaesthesia and 2.91 ± 1.09 during the biopsy (both were mild pain levels). Prior to this, there have been studies on the use of different types of local anaesthesia nerve blocks for patients undergoing TPBx to reduce perioperative and postoperative pain. Kubo et al. [13] described a periapical triangle block bounded laterally by the levator ani, the

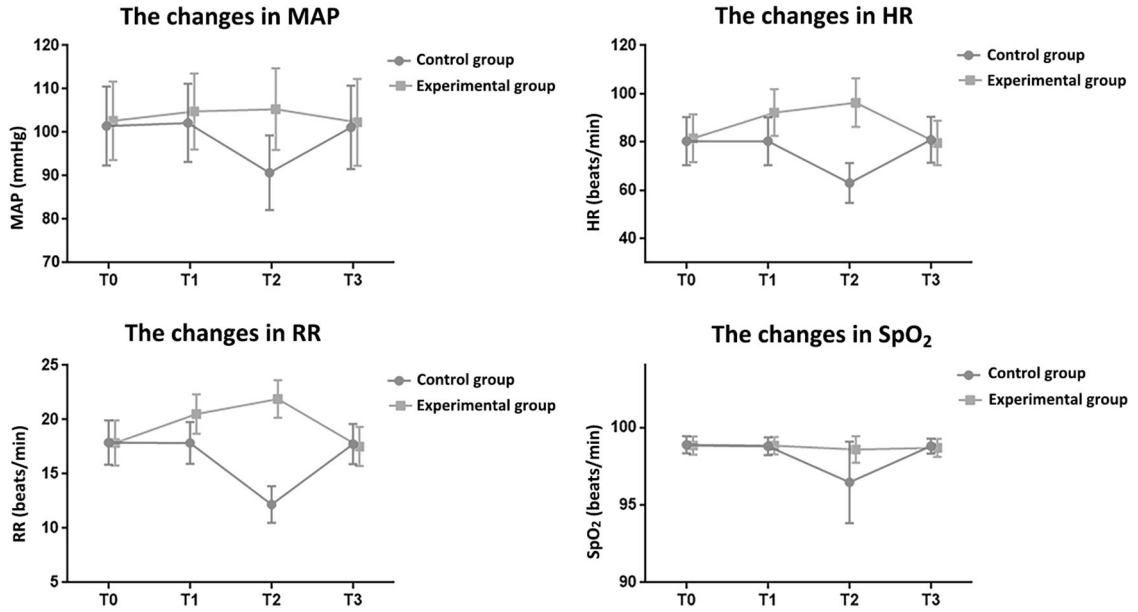

Fig. 3 The changes in vital signs in the two groups

rhabdosphincter and the external anal sphincter muscle and assessed the tolerability for patients undergoing TPBx, and they reported VAS pain scores for the biopsy procedure of 2.93 ± 1.97. Iremashvili et al. [12] performed a randomised prospective study to evaluate the effectiveness of periprostatic nerve block (PPNB) and combined PPNB with pudendal nerve block for pain control and found that the injection of the local anaesthetic agent was significantly more painful in the group with the added pudendal nerve block compared with the level of pain in the group with the periprostatic nerve block alone (2.38 ± 1.56 vs 1.72 ± 1.03), but they found a statistically significant improvement in the pain level during the biopsy (2.07 ± 1.22 vs 3.63 ± 1.71). Smith et al. [14] described their technique for subcutaneous perineal skin block combined with prostatic apex block and reported VAS pain scores for the anaesthesia procedure of 3.29 ± 1.13 and for the biopsy procedure of 2.88 ± 1.28.

The biopsy time of the experimental group was slightly longer than that of the control group (19.64 vs. 14.65 min), which could be explained by the slow and gentle manoeuvres that were necessary to relieve the discomfort caused by the rectal probe and transperineal punctures under local anaesthesia. Even so, the results showed that the experimental group method was much more efficient in terms of anaesthetic time and total operation duration ($P < 0.05$).

Regarding safety, we found that patients in the experimental group showed mild increases in their MAPs, HRs and RRs compared with the baseline values during anaesthesia and biopsy. We thought that this was mainly related to the patients' anxiety and could also be related to the low-level pain. Therefore, preoperative care should be emphasised to relieve patients' concerns. Patients should be trained to practice calming breathing during the operation and should be notified that the surgical manoeuvres will be gentle and slow. In contrast, the safety of a few patients in the control group was not optimal. We observed that many patients experienced significant reductions in their MAPs, HRs and RRs after receiving general intravenous anaesthesia. Some patients even experienced severe hypotension, low RRs and respiratory depression. This was attributed to the side effects of anaesthetic drugs. Propofol has a cardiovascular inhibitory effect that decreases peripheral vascular resistance, cardiac preload, sympathetic nerve activity and myocardial contractility [20]. Fentanyl leads to respiratory depression by interacting with the respiratory inhibitory receptors in the brainstem region [21]. The incidences of complications were also an important consideration in the analysis of safety. No significant differences were observed in the incidence rates of all complications between the study arms. It is worth noting that no patient experienced an infectious complication, which is consistent with previous reports that the rate of sepsis is less than 0.01%, with minor infectious complications also being quite rare [9, 17–19].

All patients who needed prostatic biopsies were admitted to the day surgery centre at our institute. Day surgery is defined as the process in which the patient is admitted, operated on and discharged within 1 working day [22]. The model of day surgery has developed rapidly throughout the world and has achieved high levels of acceptance and satisfaction. Day surgery can reduce medical expenses and shorten the durations of waiting and hospitalisation.

Our study has limitations. First, when VAS scoring was used to evaluate the intra-operative pain level, we could not compare the local anaesthesia and general anaesthesia groups because the latter cannot feel pain during surgery. If

we were going to objectively evaluate the level of intraoperative pain control, a placebo group would be needed. However, it was impossible to perform the puncture without anaesthesia or with a saline injection due to ethical considerations. Second, it was not possible to blind the groups and the operator. The lack of blinding may have affected the operator's perceptions and led to measurement bias in the questionnaire results. Third, the patients in the study were all Asian, so our findings should be interpreted cautiously with regard to different racial/ethnic groups. Finally, our findings were obtained at a single centre, and more convincing evidence from multiple centres is needed.

Conclusion

In the present study, we provided direct and meaningful evidence that a periprostatic nerve block combined with subcutaneous perineal anaesthesia and intrarectal lidocaine gel is a safe and efficient anaesthetic approach for transperineal prostate biopsy. This anaesthetic approach is well tolerated by patients, who maintained stable haemodynamic and respiratory statuses without any severe complications, and is worth introducing to outpatient clinics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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