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CLINICAL TRIAL REPORT

The Effect of Lidocaine-Prilocaine Cream Combined with or Without Remimazolam on VAS and APAIS Anxiety Score in Patient Undergoing Spinal Anesthesia

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Purpose: This study aimed to investigate patients' expectative pain of spinal anesthesia puncture and anxiety pre-anesthesia, and to examine the effect of lidocaine-prilocaine cream and remimazolam prior to spinal anesthesia puncture on pain relief and anxiety release.

Methods: Patients undergoing spinal anesthesia were divided into control, lidocaine-prilocaine cream, and lidocaine-prilocaine cream with remimazolam groups. A questionnaire consisting of The Amsterdam Preoperative Anxiety and Information Scale (APAIS) and patient's concerns and Visual Analog Scale (VAS) was used to evaluate patient's anxiety and pain. The primary outcomes were differences in VAS and anxiety scores. Patient's spinal anesthesia-related concerns, advent events and hemodynamic index were also recorded.

Results: The expected spinal anesthesia puncture pain was 5.34±0.27 and anxiety scores before spinal anesthesia was 10.88 ± 0.64. A statistically significant positive correlation of 31.3% was detected between VAS and APAIS scores (r = 0.313; P=0.003). The VAS score at the time of puncture decreased by 29.7% (3.78±0.40, P=0.001) in lidocaine-prilocaine cream group and 29.2% (3.75±0.39, P=0.001) in lidocaine-prilocaine cream with remimazolam group compared with the expected VAS score. Lidocaine-prilocaine cream combined with or without remimazolam reduced the percentage of moderate pain (21.4% and 31.3% vs 50.0%, P=0.0001) and increased mild pain (60.7% vs 59.4% vs 22.7%, P=0.03). Anxiety score in lidocaine-prilocaine cream group was reduced by 2.84 (8.04 ±0.76 vs 10.88 ± 0.46, P=0.05) when compared with pre-anesthesia. Concerns about postoperative pain (P=0.03) and fear of the needle or intervention (P=0.000) both decreased post-anesthesia among groups.

Conclusion: Approximately half of the patients scheduled for spinal anesthesia experienced a moderate level of preoperative anxiety. The patient's pain expectation from the spinal anesthesia puncture was moderate, which was higher than the actual pain. Lidocaine-prilocaine cream with or without remimazolam sedative before spinal anesthesia puncture reduced the patient's pain and anxiety scores after surgery.

Keywords: preoperative anxiety, APAIS, spinal anesthesia, lidocaine-prilocaine, remimazolam

Introduction

Preoperative anxiety is one of the most important problems for patients undergoing surgery, because it causes emotional, psychiatric, and physical problems.[1–3] All patients had different levels of anxiety. Preoperative anxiety includes anxiety about both anesthesia and surgery, but the exact etiology of anxiety varies from patient to patient.[4] The common reasons of patient's preoperative anxiety included insufficient perioperative information, unknown situation, detrimental effects of drugs, fear of postoperative pain, postoperative nausea and vomiting and fear of intervention etc.[5,6] Therefore, detecting a patient's existing anxiety preoperatively is critical to assist the patient. The Amsterdam Preoperative Anxiety and Information Scale (APAIS) is a practical tool to assess preoperative anxiety in patients.[7,8] This scale is

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developed specifically for surgery which is mostly used by anesthesiologists.[9] The APAIS is specific for the preoperative situation. It contains 6 specific items for the preoperative situation (including four anxiety and two need-for-information items).[7]

Anxiety is positively correlated with pain. Patients with clinically significant anxiety demonstrate lower pain tolerance than those with lower anxiety level.[10] An earlier study also demonstrated that the APAIS anxiety scores were considered independent predictors of severe pain within the first hour postoperatively.[11] Fear of pain or expectations of pain may increase a patient's preoperative anxiety.[5] Spinal anesthesia is one of the most commonly used anesthesia methods in clinical practice. Pain during spinal anesthesia should be managed carefully as this would affect the perception and comfort of patients and thus increase their anxiety levels.[12] Needle-related pain is one of the reasons why patients refuse spinal anesthesia.[13] Pain associated with spinal puncture may cause involuntary movement, which often disturbs the patient's posture and may affect the success of spinal anesthesia. Reducing pain during spinal puncture may improve the quality of anesthesia. Additionally, the patient would have a positive experience during the anesthesia procedure.

Comfort Theory was proposed by Kolcaba et al[14,15] Interventions designed to enhance comfort in one aspect can have a larger effect on total comfort than expected. Particular emphasis is placed on interventions to treat anxiety, as this discomfort can be severe and negatively impacts physiological functioning. Therefore, we advocate advanced comfortable anesthesia, allowing patients to undergo an invasive pain puncture in painless. Eutectic mixtures of local anesthetics (EMLAs) have recently become available for pain relief during spinal anesthesia injections.[12,16–18] An EMLA is formulated to penetrate intact skin and significantly reduces puncture pain. Lidocaine-prilocaine is an EMLAs used for pain relief during local procedures or surgeries.[19,20] Lidocaine-prilocaine cream possesses superior skin permeability and therefore provides adequate anesthesia. Various sedatives such as dexmedetomidine, propofol and benzodiazepines have been used to release patient's anxiety during the surgery but not before the anesthesia. In this study, we try to sedative patients before spinal anesthesia puncture to release their anxiety. Remimazolam, a benzodiazepine sedative, was used to relieve patient's anxiety during anesthesia. It has been approved in the USA and EU for the induction and maintenance of procedural sedation in adults. Procedural sedation may be administered to patients to improve comfort during diagnostic or therapeutic procedures.[21,22]

In this study, we combined lidocaine–prilocaine cream and remimazolam before spinal anesthesia puncture to relieve needle-related puncture pain and patient anxiety. A questionnaire consisting of the APAIS and patient's concerns about anesthesia was used to evaluate the patient's anxiety, and the Visual Analog Scale (VAS) was used to assess the patient's puncture pain. This study aimed to investigate patients' expectative pain of spinal anesthesia puncture and anxiety pre-anesthesia, and to examine the effect of combined use of lidocaine-prilocaine cream and remimazolam prior to spinal anesthesia puncture on pain relief and anxiety release. We hypothesized that lidocaine-prilocaine cream combined with remimazolam before spinal anesthesia puncture reduced the patient's pain and anxiety scores.

Materials and Methods

Ethics and Trial Registration

The trial was conducted between June and September 2023 in the First Affiliated Hospital of Jinan University. This study has been conducted in accordance with the requirements of laws and regulations, as well as the general principles of international ethical guidelines for biomedical research involving human subjects and the Declaration of Helsinki. This prospective, randomized, controlled study was performed after obtaining approval from the Institutional Review Board of the First Affiliated Hospital of Jinan University (KY-2023-112;03/23/2023) and written informed consent from each patient. The protocol for this clinical trial is registered in the Chinese Clinical Trial Registry (ChiCTR2300069970).

Inclusion and Exclusion Criteria

Patients scheduled for surgery with spinal anesthesia received a predesigned questionnaire and finished in 10 min with the help of nurses. Patients were required to meet the following criteria: 18–60 years of age, BMI 18–30 kg/m^2, American Society of Anesthesiologists Physical Status (ASA PS) I to II, elementary school education or higher, no

reading or hearing disability, and have ability to sign an informed consent form. The exclusion criteria were as follows: (i) history of unregulated diabetes, hypertension, and hypotension; (ii) myocardial infarction within 6 months or unstable angina pectoris; (iii) III degree atrioventricular block; (iv) severe snoring; (v) sleep apnea syndrome; (vi) decompensated liver function or renal function; (vii) dialysis treatment; (viii) psychosocial disease or cognitive dysfunction; (ix) history of psychotropic and narcotic drug abuse; (x) allergy to or contraindications to the drugs used in this study; (xi) participation in clinical trials of other drugs within 3 months.

Randomization and Blinding

According to literature, a VAS score decrease of 20% was considered effective in relieving pain, and the inspection efficiency was set at 0.80, whereas the inspection level was set at 0.05. Considering a loss rate of 10%, a required total sample size of 90 was calculated using PASS 11 software (NCSS, Kaysville, Utah). The random sequence generator of SPSS software generated 90 random numbers and divided them into three groups. The patients were assigned to control group (performed spinal anesthesia following the standard operation procedure), topical anesthesia group (lidocaine-prilocaine cream before spinal anesthesia), and topical and sedative anesthesia group (lidocaine-prilocaine cream and remimazolam before spinal anesthesia) according to the random numbers by the researcher who performed randomization. Blinded anesthesiologists were given syringes with clear solutions in the same bottles with codes, according to the randomization order. The researcher who performed the randomization and blinding procedures did not participate in the follow-up study. Other investigators were not informed of the grouping or experimental drugs. To ensure allocation concealment, the randomization results were sealed until the end of the study.

Anesthesia Sedation Process

Patients were educated on the procedure of spinal anesthesia during the preoperative visit. The patient fasted after midnight, and no prior medication was administered. Patients received and completed the questionnaire in 10 min with the help of nurses once they entered the waiting room for surgery. Expected spinal anesthesia puncture pain was evaluated using the VAS. The questionnaire consists of three parts. The first part asked about the patient's general information. The second part, which included 4 questions, was the anxiety score from the APAIS. The APAIS comprises of six statements. The answers were evaluated on two scales: anxiety and the desire for information. In this study, we evaluated patient's anxiety scores using four statements from the APAIS. Anxiety score was obtained by calculating the total scores assigned to the expressions "I am worried about the anesthesia", "The anesthesia is on my mind continually", "I am worried about the procedure", "The procedure is on my mind continually", to measure the patient's level of anxiety regarding the anesthesia and surgery. The last part is patient's concerns regarding spinal anesthesia. The questionnaire was completed for second time after surgery. The Cronbach's alpha coefficients for the 30 items for the anxiety score and anesthesia-related concerns before and after spinal anesthesia were 0.899 and 0.845, respectively, and the overall coefficients were 0.914. These coefficients are in good agreement with the 0.87 coefficients reported by Aust et al.[4]

After completing the survey, patients were randomized into three groups using computer generated random numbers. The procedure of spinal anesthesia is shown in Figure 1. A 22 G intravenous cannula was inserted via the vein for fluid infusion. Standard monitoring, including blood pressure (BP), heart rate (HR), and pulse oximetry (SPO_2), was recorded at the time the patient entered the operation room(T1). Oxygen supplementation at 2 L/min was administered via a nasopharyngeal tube throughout the study. Approximately 5 g of lidocaine-prilocaine cream or moisturizing cream was applied to the spinal anesthesia puncture site and covered with a transparent membrane for at least 30 min before spinal anesthesia. A blinded anesthesiologist with at least 5 year-experience on spinal anesthesia performed spinal anesthesia. 0.5 mg/kg remimazolam (1 mg/mL) or the same volume of normal saline was administered via an intravenous cannula for sedation. Two minutes after sedation, an anesthesiologist assessed the Ramsay sedation score. The expective Ramsay sedation score was 2–3. A Ramsay score of ≥ 4 was considered sedated, and we waited for the patient to recover to a Ramsay score of ≤ 3 and recorded the time of recovery. BP, HR, and SPO_2 were recorded immediately after assessment of the Ramsay sedation score(T2). A blinded anesthesiologist performed the spinal anesthesia for the patients following the standard operation procedure of the department of anesthesiology in the hospital. When the needle punctured the skin, patients were asked to evaluate pain using the VAS and BP, HR, and SPO_2 were recorded(T3). BP, HR, and SPO_2 were

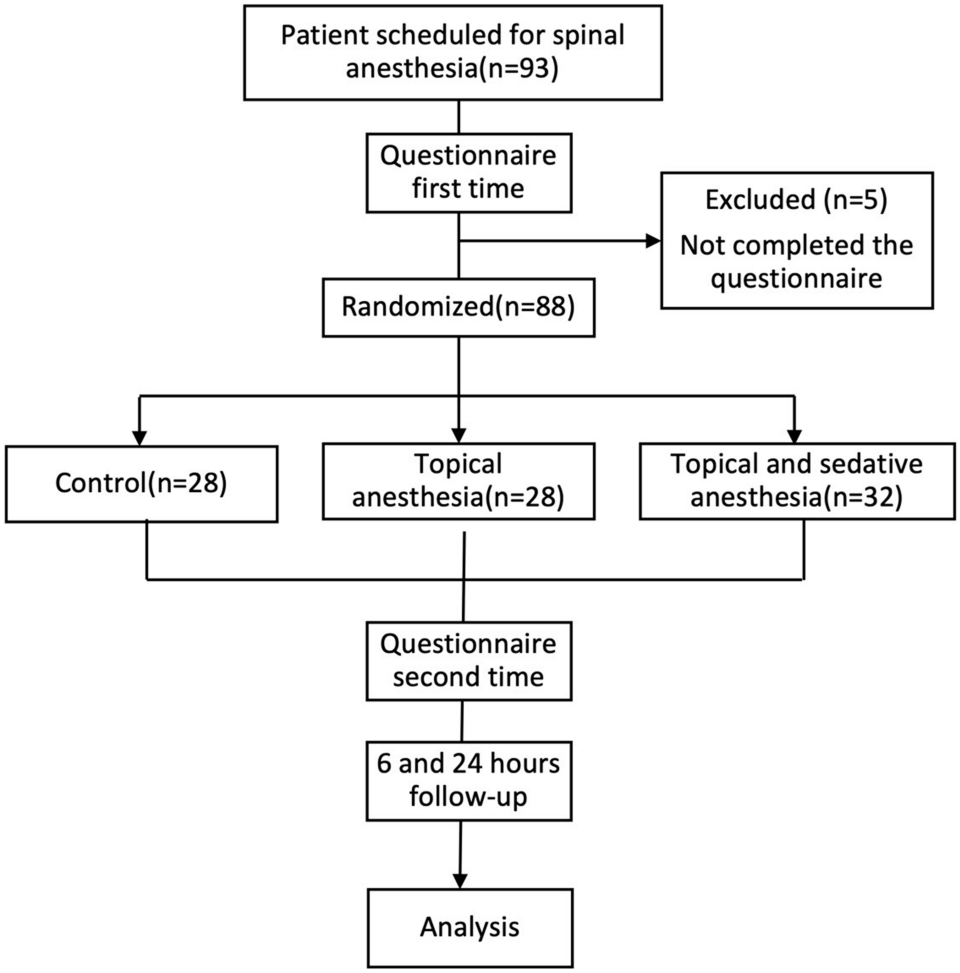

Figure 1 Flow diagram. A total of 93 patients who fulfilled the inclusion criteria were invited to participate in the study. 5 participants did not complete the questionnaire and 88 of these patients completed and returned the questionnaires were analyzed.

recorded after spinal anesthesia(T4), at the beginning of the surgery(T5), 5 min after the surgery(T6), and at the end of the surgery(T7). A nurse followed up with the patients 6 and 24 h after surgery, and adverse events were recorded.

Primary and Secondary Outcome

The primary outcomes were differences in VAS and anxiety scores before and after spinal anesthesia the three groups. The secondary outcomes included spinal anesthesia-related concerns, incidence of postoperative nausea and vomiting, sedation, respiratory depression, dizziness, and hemodynamic index. Patients with a Ramsay sedation score≥ 4 were considered sedated. Respiratory depression was defined as oxygen saturation <90%.

Statistical Analysis

Data analysis was performed using SPSS (version 13.0; IBM Corporation, Armonk, NY, USA) for Windows. Demographic data of patients were collected and analyzed with descriptive statistics. The percentage of agreement was calculated as the percentage of participants who scored from 1 to 5 for each question. Categorical variables were described using number (%) and compared using Pearson's chi-square test or Fisher's exact test. Quantitative variables were expressed as means and standard deviations, and normally distributed variables were compared using ANOVA followed by Tukey's test. Variables that were not normally distributed were compared using the Mann–Whitney *U*-test. A P-value ≤ 0.05 or less was regarded as statistically significant.

Results

Demographics of Study Participants

The demographic characteristics of the patients who underwent surgery with spinal anesthesia are presented in Table 1. A total of 93 patients who fulfilled the inclusion criteria were invited to participate in the study. 88 of these patients completed and returned the questionnaires before anesthesia. The response rate was 94.6%. Most responses were from women (70.5%), with ages ranging from 22 to 60 and a mean age of 39.7±1.0. Most patients had a college education (56.8%). A total of 26.1% of the participants had experienced spinal anesthesia.

Patient's Expective VAS Score and Anxiety Score Before Spinal Anesthesia

Spinal anesthesia puncture pain was evaluated by VAS, and our patient's expectation before anesthesia was 5.34±0.27. VAS score between 4–6 is defined as moderate pain.

Anxiety scores evaluated by APAIS of our patients before spinal anesthesia ranged between 4 and 20, and the mean was 10.88 ± 0.64. Of our patients, 26.1% were assigned to "I am worried about the anesthesia", 21.6% assigned to "The anesthesia is on my mind continually", 38.6% assigned to "I am worried about the procedure", and 25.2% assigned to "The procedure is on my mind continually". A statistically significant positive correlation of 31.3% was detected between VAS and APAIS scores (r = 0.313; P=0.003). The distribution regarding "The Amsterdam Preoperative Anxiety and Information Scale (APAIS)" of the cases is given in Figure 2.

Patients Concerns About Spinal Anesthesia Before the Procedure

We asked the patients about spinal anesthesia-related concerns twice. Before anesthesia was performed, 42 patients (47.37%) were anxious about postoperative pain and 47.37% (n = 42) were fear of the needle and intervention. We demonstrate other reasons of concerns in Figure 3.

Demographics of Participants Among Three Groups

As per our study design, 88 patients who completed and returned the questionnaire were divided into three groups: control, topical anesthesia, and topical and sedative anesthesia. The demographic characteristics of the patients in the

Table 1 Demography Data of All Patients (N=88)

	Number	Percentage (%)
Gender		
Female	62	70.5
Male	26	29.5
Age, years		
18–30	17	19.3
31–50	60	68.2
51–60	11	12.5
Education		
Primary school	8	9.1
Middle school	14	15.9
High school	16	18.2
College	50	56.8
Surgery type		
Haemorrhoid surgery	41	46.6
Endocervicectomy	22	25.0
Hysteroscopic surgery	18	20.4
Lower extremity surgery	7	8.0
Experience of spinal anesthesia	23	26.1

Note: Data are presented as number (%).

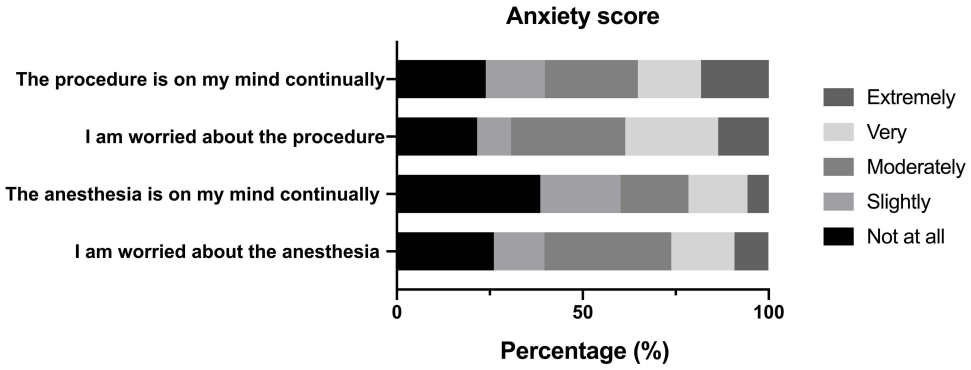

Figure 2 The distribution regarding APAIS before anesthesia of patients. Patients valued very or extremely were considered to be worried about the statement. 26.1% of our patients assigned to "I am worried about the anesthesia", 21.6% assigned to "The anesthesia is on my mind continually", 38.6% assigned to "I am worried about the procedure", and 25.2% assigned to "The procedure is on my mind continually".

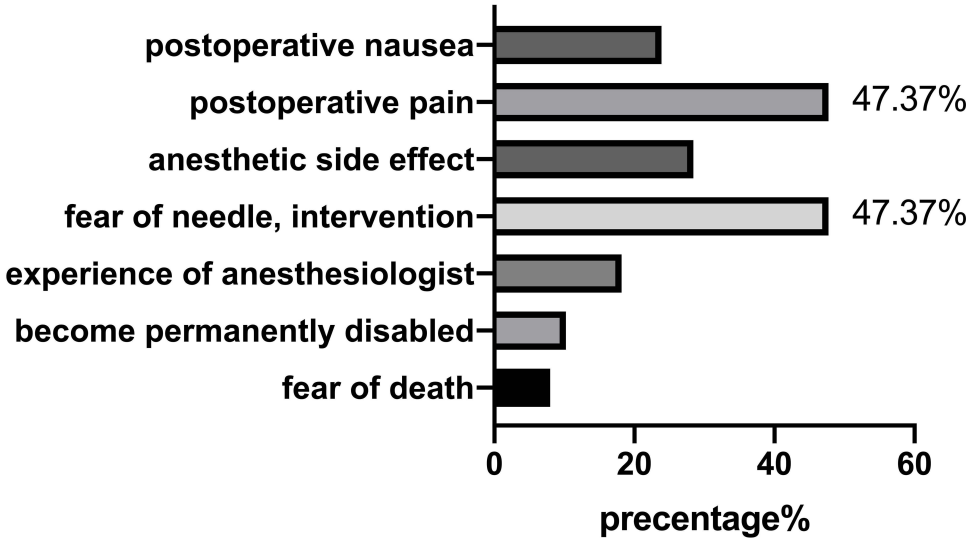

Figure 3 Anesthesia related concerns before spinal anesthesia. Patients concerned about postoperative pain (47.37%) and fear of needle, intervention (47.37%) most. 23.86% of our patients worried about postoperative nausea, 28.41% worried about anesthetic side effect, 18.18% worried about experience of anesthesiologist, 10.23% worried about become permanently disabled and 7.95% fear of death.

three groups are shown in Table 2. No significant differences were observed in the demographic characteristics of the groups.

Comparison of Spinal Anesthesia Puncture-Related Pain Assessed by VAS Between Patient's Expectation and Actual Pain

Among the 88 patients, the overall expected VAS score was 5.34±0.27. The VAS score at the time of puncture decreased by 29.7% (3.78±0.40, P=0.001) in the topical anesthesia group and 29.2% (3.75±0.39, P=0.001) in the topical and sedative anesthesia group compared with the expected VAS score before anesthesia puncture. However, there was no significant difference in the VAS scores between the control group and patients' expectation. Pain reduction results are shown in Table 3.

A VAS score of 1–3 was defined as mild pain, 4–6 as moderate pain and 7–10 as severe pain, and 0 as no pain. Topical anesthesia or topical and sedative anesthesia reduced the percentage of moderate pain (21.4% and 31.3% vs 50.0%, P=0.0001) and increased mild pain (60.7% and 59.4% vs 22.7%, P=0.03), but there was no significant difference in severe pain. (Figure 4).

Table 2 Patient Demography Data of Three Groups

	Control (N=28)		Topical anesthesia (N=28)		Topical anesthesia and sedative(N=32)		P value
	Number	Percentage	Number	Percentage	Number	Percentage	
Gender							0.401
Female	17	60.7	21	75.0	24	75.0	
Male	11	39.3	7	25.0	8	25.0	
Age, years							0.096
18–30	4	14.3	7	25.0	6	18.8	
31–50	17	60.7	20	71.4	23	71.9	
51–60	7	25.0	1	3.6	3	9.4	
Education							0.202
Primary school	4	14.3	1	3.6	3	9.4	
Middle school	5	17.8	2	7.1	7	21.9	
High school	1	3.6	7	25.0	8	25.0	
College	18	64.3	18	64.3	14	43.7	
Surgery type							0.260
Haemorrhoid surgery	17	60.6	11	39.3	13	40.6	
Endocervicectomy	5	17.9	7	25.0	10	31.3	
Hysteroscopic surgery	5	17.9	8	28.6	5	15.6	
Lower extremity surgery	1	3.6	2	7.1	4	12.5	
Experience of spinal anesthesia	6	21.4	9	32.1	8	25.0	0.941

Note: Data are presented as number (%).

Table 3 Patient's VAS Score Before and After Anesthesia

Expectative VAS score	VAS Score After Anesthesia			P value
	Control	Topical Anesthesia	Topical and Sedative Anesthesia	
5.34±0.27	4.10±0.40	3.78±0.40*	3.75±0.39*	0.001

Notes: Data are presented as mean ± SD. *P<0.05 compared with expectative VAS score.

Anxiety Score by APAIS Decreased After Spinal Anesthesia

We evaluated the patient's anxiety score using the APAIS twice: before and after spinal anesthesia. The post-anesthesia anxiety scores ranged between 4 and 14, 4 and 17, and 4 and 18 among the three groups, respectively (Table 4). Anxiety score in topical anesthesia group was reduced by 2.84 (8.04±0.76 vs 10.88 ± 0.46, P=0.05) when compared with pre-anesthesia.

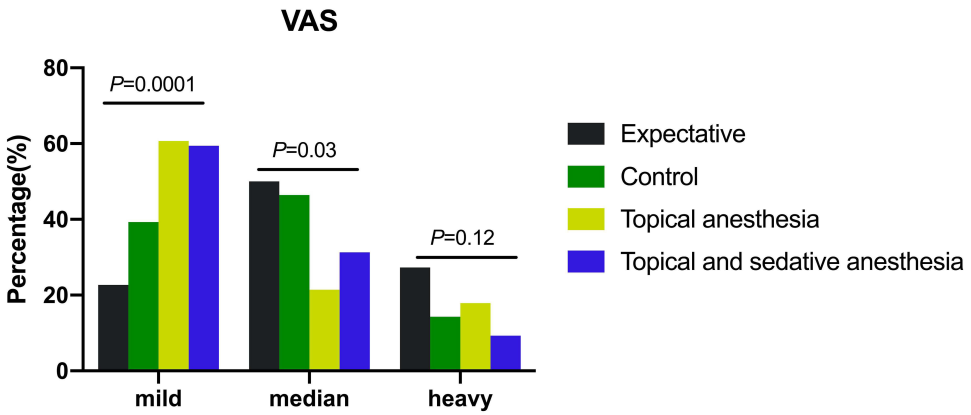

Figure 4 The percentage of patient's VAS score. VAS score between 1–3 is defined as mild pain, 4–6 as moderate pain and 7–10 as severe pain, and 0 as no pain. Topical anesthesia or topical and sedative anesthesia reduced the percentage of moderate pain (21.4% and 31.3% vs 50.0%, P=0.0001) while increased the mild pain (60.7% and 59.4% vs 22.7%, P=0.03), but there was no significant difference in severe pain.

Table 4 Pre-Anesthesia and Post-Anesthesia APAIS Scores

	Pre-Anesthesia	Control	Topical Anesthesia	Topical and Sedative Anesthesia	P value
Range	4–20	4–14	4–17	4–18	
Mean±SD	10.88 ± 0.46	7.28±0.81*	8.04±0.76*	9.34±0.73	0.001
Worried about anesthesia	26.1%	14.2%*	5.3%**	8.7%*	0.000

Notes: Data are presented as mean ± SD or number (%). *P<0.05 compared with pre-anesthesia, **P<0.01 compared with pre-anesthesia.

The distribution of APAIS post-anesthesia in these cases is shown in Figure 5. 14.2%, 5.3% and 8.7% of the patients in control group, topical anesthesia group and topical and sedative anesthesia group, respectively, worried about the anesthesia.

Spinal Anesthesia-Related Concerns Before and After the Procedure

After spinal anesthesia, we asked our patients about spinal anesthesia-related concerns again. Concerns about post-operative pain (P=0.03) and fear of the needle or intervention (P=0.000) both decreased post-anesthesia among the three groups. Other reasons of concerns are listed in Table 5.

Hemodynamics Data and Adverse Events

Since we administered lidocaine cream with or without remimazolam before spinal anesthesia, we assessed hemodynamic data and adverse events in our patients for safety (Figure 6). Heart rate was higher in the topical and sedative groups than in the control group (71.6 vs 74.6, P=0.04). No statistically significant differences were detected in SBP, DBP, or SPO_2 among the three groups (P > 0.05). None of the patients in either group was desaturated with oxygen (oxygen saturation <90%) during the study period. However, we observed that one patient became too sedated (Ramsay sedation score ≥ 4), this patient recovered approximately 2 min after the administration of remimazolam and Ramsay sedation score = 3. Adverse effects, such as postoperative sedation, respiratory depression, and drowsiness, did not differ between the groups.

Discussion

In our study, we aimed to evaluate patients' pain using VAS and anxiety using the APAIS scale, and to relieve patient's pain and anxiety before anesthesia to achieve the goal of advanced comfort anesthesia. Patients undergoing spinal anesthesia are concerned about postoperative pain and fear of the puncture needles. Patients' expectations for puncture pain and pre-anesthesia anxiety were moderate. Topical anesthesia with lidocaine-prilocaine cream before spinal anesthesia puncture, with or without remimazolam sedation, reduced the patient's pain and lowered their postoperative anxiety score.

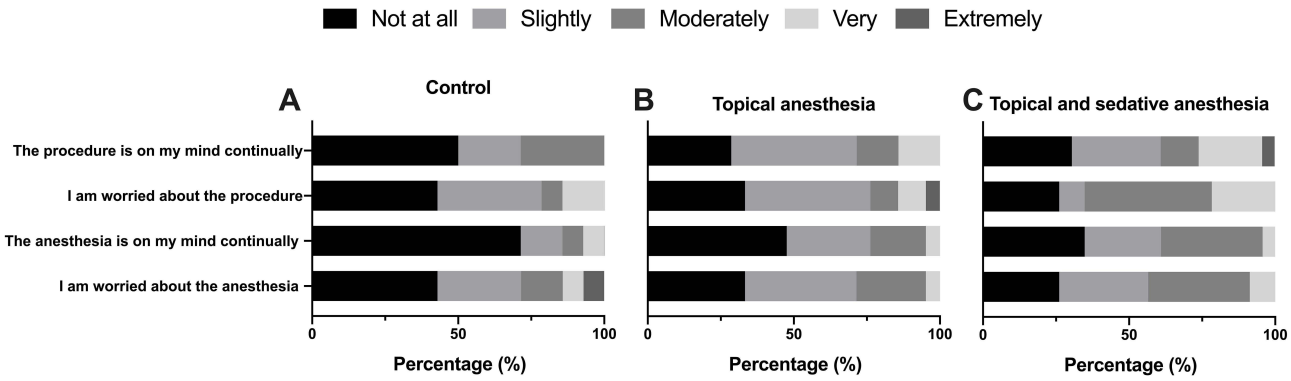

Figure 5 The distribution regarding APAIS post-anesthesia of patients. Patients valued very or extremely were considered to be worried about the statement. 14.2%, 5.3% and 8.7% of the patients in control group (**A**), topical anesthesia group (**B**) and topical and sedative anesthesia group (**C**), respectively, worried about the anesthesia.

Table 5 Spinal Anesthesia-Related Concerns Before and After the Procedure

	Expectative Concerns	Control	Topical Anesthesia	Topical and Sedative Anesthesia	Chi-Square	P value
Postoperative nausea	23.86% (21)	10.71% (3)	10.71% (3)	15.63% (5)	4.15	0.245
Postoperative pain	47.73% (42)	28.57% (8)*	25% (7)*	25% (8)*	8.91	0.030
Anesthetic side effect	28.41% (25)	10.71% (3)	14.29% (4)	25% (8)	5.15	0.161
Fear of needle and intervention	47.73% (42)	10.71% (3)**	21.43% (6)*	12.5% (4)**	23.11	0.000
Experience of anesthesiologist	18.18% (16)	10.71% (3)	0.00% (0)	6.25% (2)	7.17	0.054
Become permanently disabled	10.23% (9)	7.14% (2)	7.14% (2)	9.38% (3)	0.335	1.000
Fear of death	7.95% (7)	7.14% (2)	7.14% (2)	9.38% (3)	0.321	0.975

Notes: Data are presented as percentage (N). *P<0.05 compared with expectative concerns, **P<0.01 compared with expectative concerns.

Preoperative Anxiety is Common in Patients Underwent Surgery and Anesthesia

Anxiety was common preoperatively. A study of 3087 participants showed that the mean total preoperative anxiety score was 9.9 ± 3.6.[3] Anxiety scores evaluated by APAIS of our patients before spinal anesthesia ranged between 4 and 20, and the mean score was 10.88 ± 0.64. According to an observational study of more than 15,000 patients undergoing a non-obstetric surgical procedure, anxiety was most frequently mentioned as the worst aspect of the perioperative period.[23] Patients were worried about not only the operation but also anesthesia preoperatively. Almost half of our patients were

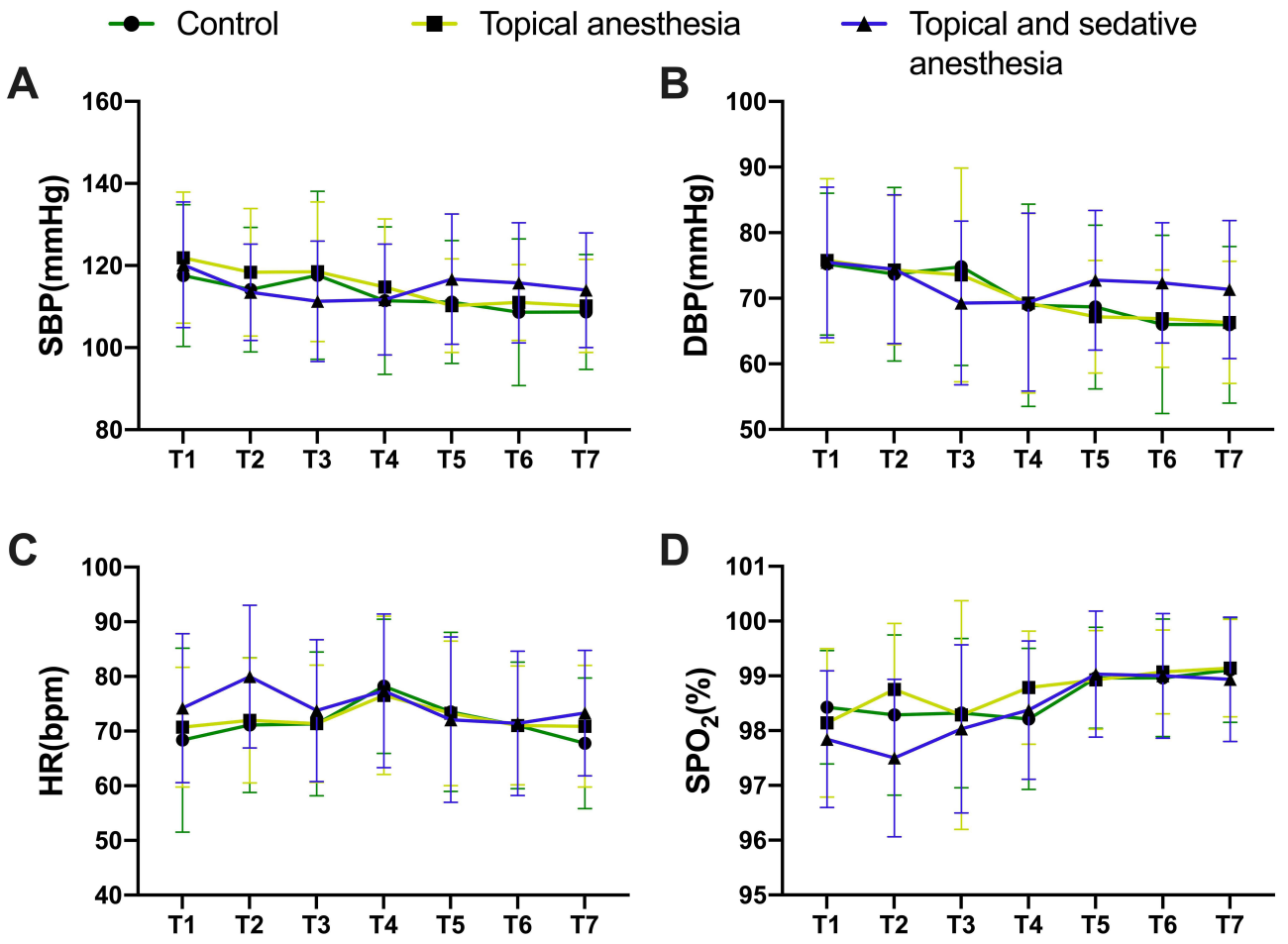

Figure 6 The results of repeated measurements of hemodynamic parameters. Systolic blood pressure (**A**), diastolic blood pressure (**B**), heart rate (**C**), and pulse oximetry (**D**) of patients in control, topical anesthesia and topical and sedative anesthesia groups.

worried about the anesthesia preoperatively. Two studies also reported that patients had fears related to anesthesia.[24,25] To help patients with their anesthesia related anxiety, it may be helpful to be familiar with all the relevance of specific fears associated with anesthesia related anxiety from patient's perspective. The most common reasons for fear were post-operative pain, not awakening from anesthesia, delayed wound healing, wound infection, inability to take care of children, uncertainty about the future, inability to perform daily routines, economic losses, fear of death, fear of physical disability, and waking up during surgery.[2,8,26] Patients were anxious about spinal anesthesia needle puncture and postoperative pain most before spinal anesthesia in our study. Besides concerns about pain, patients were worried about postoperative nausea, anesthetic side effects, become permanently disabled and fear of death. The percentages of these concerns ranged from 6% to 28% among our patients. These problems are important reasons why patients feel anxious during the operation. Therefore, preoperative education should pay attention not only to the patient's pain but also to other concerns related to anesthesia. Our previous study also showed that in patients' perceptions, details about anesthesia are the most important information in preoperative education.[27] Furthermore, preoperative education about anesthesia should be tailored according to the patient's demands to relieve their anxiety. King[28] and Stefan[5] also argue against the idea that one can support every patient by providing standardized information, and they both argued for the importance of tailored care offering support depending on an individual patient's needs.

Patient's Anxiety is Related with Pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[29] Anxiety is associated with an increased perception of pain severity, and this relationship is consistent across studies, as increased anxiety leads to an increased severity of perceived pain and decreased pain tolerance.[30–32]Our study found a positive correlation between expected pain and anxiety, and higher anxiety scores were related to higher VAS scores preoperatively. Carr et al[32] also showed that anxiety is positively correlated with pain. This may be due to the fact that the higher the level of anxiety, the greater the concern for environmental threats and perceived pain.[31] On the other hand, pain is also related with anxiety. Patients' expectations of pain, needle puncture pain, or postoperative pain increase their anxiety preoperatively. Kim et al reported that pain during spinal injections had a mean pain scale of 3.9 based on the Numeric Pain Rating Scale.[31] In our study, the VAS score at the time of puncture was lower than the expected VAS score before the anesthesia puncture. The overall expected VAS score of the spinal injections was 5.34±0.27, and the actual pain of needle puncture was 4.10±0.40. We asked patients about anesthesia-related concerns. Patients were mostly anxious about concerns related to pain, and the percentage of these concerns decreased post-anesthesia. According to APAIS, patient's worry about anesthesia decreased from 26.1% to 14.2% and APAIS of our patients before spinal anesthesia was 10.88 ± 0.64 which decreased to 7.28±0.81 postoperatively. Patients' expectations of pain are higher than their actual pain, which leads to a higher level of preoperative anxiety.

Lidocaine-Prilocaine Cream with or Without Remimazolam Sedative Before Spinal Anesthesia Puncture Reduced Patient's Pain and Decreased Their Anxiety Level

Since we found that patients were anxious and fearful of needle puncture preoperatively, it is essential to relieve the patient's pain and anxiety to achieve advanced comfort anesthesia.

Lidocaine-prilocaine cream is a type of EMLAs used for pain relief during local procedures and surgeries.[12,19] Apply lidocaine-prilocaine cream at the skin of puncture site for at least 30 minutes as topical anesthesia can reduces puncture pain. The success of spinal anesthesia relies not only on the anesthesiologist's technique but also on the patient's cooperation. Pain associated with spinal anesthesia may cause involuntary movement, which often disturbs the patient's posture and may affect the success of spinal anesthesia.[33] In our study, the VAS score at the time of spinal anesthesia puncture decreased in the topical anesthesia group with or without remimazolam. Furthermore, topical anesthesia with lidocaine-prilocaine cream reduced the percentage of moderate pain and increased the percentage of mild pain in our patients. However, there was no significant difference in the percentage of severe pain. As mentioned above, patients with higher anxiety levels have lower tolerance to pain.[10,30] The high level of anxiety may explain why patients with severe pain scores did not experience significant pain relief after using lidocaine-prilocaine cream.

Therefore, in this study, we attempted to use remimazolam to alleviate patient anxiety before the spinal anesthesia. Remimazolam, which acts on gamma-aminobutyric acid receptors, is a new ultrashort acting benzodiazepine. It offers more rapid recovery and earlier restoration of cognitive function.[22] Midazolam is a sedative with antianxiety properties. It is the most frequently used benzodiazepine for patients with high anxiety or phobia.[34] Research has evaluated remimazolam on Modified Dental Anxiety Scale scores, and the results showed that remimazolam reduced anxiety scores after surgery compared with before surgery.[35] In this study, our results also showed that remimazolam reduced APAIS after anesthesia compared to pre-anesthesia, and patients in the remimazolam group worried less about anesthesia. However, we did not observe any differences in the anxiety scores among the three groups. The dose of remimazolam we used in this study did not reduce patient's anxiety on the basic of topical anesthesia. In this study, 0.05 mg/kg of remimazolam was administered. The effects of sedation and antianxiety levels did not meet our expectations because of the low dose of remimazolam used in this study. Despite spinal anesthesia needle puncture pain, patients were also concerned about postoperative nausea, anesthetic side effects, become permanently disabled and fear of death in our study. Although these concerns were not the most serious of all anesthesia-related problems, they did not improve after anesthesia in our study. Thus, patient's anxiety is not only related to pain but also to other aspects. In future studies, different doses of remimazolam should be evaluated to relieve anxiety, and the complete picture of patients' specific concerns and fears can help with a better understanding of preoperative anxiety.

Limitation

There are still some limitations to our study. First, the dose of remimazolam set in this study was relatively low. Additional studies with different doses of remimazolam can be considered. Second, approximately 5 g of lidocaine-prilocaine cream was applied to the spinal anesthesia puncture site at least 30 min before spinal anesthesia in this study. To enhance the effectiveness of lidocaine-prilocaine cream, a longer duration of topical anesthesia may provide better relief from puncture pain. Third, the follow-up time of our study was 24 hours, extending this follow-up duration could offer a clearer understanding of patients' individual concerns and fears. Finally, multicenter studies with larger sample sizes are needed to confirm our findings.

Conclusion

In conclusion, approximately half of the patients scheduled for spinal anesthesia experienced a moderate level of preoperative anxiety. The patient's pain expectation of spinal anesthesia puncture was moderate, and the expectation was higher than the actual pain. Topical anesthesia with lidocaine-prilocaine cream with or without remimazolam sedative before spinal anesthesia puncture reduced the patient's pain and anxiety scores after surgery.

Data Sharing Statement

We would like to share individual deidentified participant data with other reseachers. The data that support the findings of this study are available upon reasonable request. Researchers interested in accessing the data should contact Shuqing Liang with email: liangsq@jnu.edu.cn for further information and data sharing arrangements.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosures

The authors report no conflicts of interest in this work.

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