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Original Research Article

Effect of the of remazolam toluenesulfonate and IPACK on postoperative rehabilitation and sedation in elderly patients undergoing knee arthroplasty

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Abstract

Purpose: *To investigate the effect of the combination of remazolam toluenesulfonate and infiltration between the popliteal artery and capsule of the knee (IPACK) on the rehabilitation and sedation of elderly patients undergoing knee arthroplasty.*
Methods: *A total of 84 elderly patients who underwent knee arthroplasty in Quzhou Affiliated Hospital of Wenzhou Medical University between January 2021 and December 2021 were given IPACK in combination with adductor canal block under ultrasound guidance. Forty (40) patients were given anesthesia with propofol + sufentanil + cis-benzene sulfonic acid atracurium (control group), while 44 patients received anesthesia with remazolam toluenesulfonate + sufentanil + cis-benzene sulfonic acid atracurium (study group). Various clinical indices in the patients were assessed*
Results: *Relative to control, there were significantly lower visual analog scale (VAS) scores at 6 and 12 h after operation, lower frequency of post-operation pumping with PCA pump, lower frequency of remedial analgesia within 48 h after operation ($p < 0.05$). Moreover, the time taken for spontaneous recovery of breathing, recovery time, and extubation time were similar in the two groups ($p > 0.05$). The muscle strength of quadriceps femoris of the affected knee joint was higher in the study group than in the control group at 12, 24, and 48 h, after operation ($p < 0.05$).*
Conclusion: *The combination of remazolam toluenesulfonate with IPACK effectively alleviate pain in elderly patients undergoing knee arthroplasty and improves sedation without increasing cognitive dysfunction. This treatment strategy has potentials for further investigation for possible large-scale application.*

Keywords: *Remazolam toluenesulfonate, IPACK, Knee arthroplasty*

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INTRODUCTION

A growing number of elderly patients undergo total knee arthroplasty (TKA) for end-stage osteoarthritis of knee joint [1]. This is the primary clinical treatment regimen for knee osteoarthritis. It has been reported that approximately 2 million patients have undergone TKA worldwide [1]. With improvements in the design of implants, surgical techniques and patients' understanding of the concept of TKA, it has been estimated that

the number of patients undergoing TKA will increase 5 folds by 2025. However, due to its highly complicated anatomical structure, the knee joint has a highly intricate mode of movement which requires very high standards in surgery involving the replacement of knee joint with prosthesis, and the operation is difficult. Moreover, TKA takes a long time, and it involves extensive peeling of skin, cutting of tissues and trimming of bone surfaces. Most of the patients are the elderly who often have comorbidities such as hypertension, coronary heart disease, and chronic obstructive pulmonary disease [1]. Thus, the selected method of anesthesia should be safe, effective and reliable, with limited adverse effects.

The sensory nerve in the human knee joint is highly complex. Pain in patients undergoing TKA after operation is controlled via the femoral, obturator and sciatic nerves. Blockage of these nerves effectively achieves analgesia during and after TKA operation. However, it is usually very difficult to completely block these nerves in order to relieve pain without affecting muscle movement [2]. Adductor canal block is a simplified sensory nerve block which only reduces the muscle strength of quadriceps femoris by 8 %, but markedly retains the movement function and balance [3]. Infiltration between the popliteal artery and capsule of the knee (IPACK) blocks the sensory nerves innervating the joint branches of the common peroneal, tibial and obturator nerves in the posterior part of the knee joint, and inhibits the pain in the posterior part of the knee joint without compromising the function of the lower limb. This is conducive for early postoperative functional exercise. However, with nerve block alone, the operation can hardly be completed without the use of general anesthesia.

Artificial airway can be quickly established under laryngeal mask general anesthesia which is easy to operate. This mode of anesthesia has been extensively adopted in clinical practice [4]. Remazolam toluenesulfonate, a benzodiazepine anesthetic sedative, binds quickly to its receptor. It has a short half-life; its cellular metabolism is independent of cytochrome P450 enzyme metabolism in cells, and its dose-related half-life is not prolonged after continuous pumping is stopped [5]. In contrast to midazolam and propofol which are frequently used as anaesthetic sedatives, remazolam toluenesulfonate has the advantages of quick effect, low influence on respiratory cycle, quick metabolism, inactive metabolites, weak interaction with drugs, and rapid reversal of its effect with flumazenil [6].

This study investigated the effect of the combination of remazolam toluenesulfonate and IPACK on postoperative rehabilitation and sedation in elderly patients undergoing knee arthroplasty. This was with a view to providing additional reference information for the selection of anesthesia scheme in these patients.

METHODS

Clinical profile of patients

A total of 84 elderly patients who underwent knee arthroplasty in the Quzhou Affiliated Hospital of Wenzhou Medical University between January 2021 and December 2021 were selected and given IPACK in combination with adductor canal block under ultrasound guidance. Forty (40) patients were given propofol + sufentanil + cis-benzene sulfonic acid atracurium (control group), while the 44 patients in the study group received anesthesia with remazolam toluenesulfonate + sufentanil + cis-benzene sulfonic acid atracurium. This study was approved by the Medical Ethics Committee of Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou People`s Hospital (approval no. QZH9875) and was conducted in line with the guidelines in the declaration of Helsinki [7].

Inclusion criteria

Patients who were diagnosed and treated in the Quzhou Affiliated Hospital of Wenzhou Medical University hospital, and who were not transferred to the hospital mid-way, patients who met the indications of TKA, those at ASA grades I-II, and patients who signed informed consent forms after understanding the protocols involved in the study, were included.

Exclusion criteria

The excluded patients were those with contraindications to nerve block anesthesia or drugs involved in this study, patients with severe comorbid systemic diseases or major organ dysfunction, as well as those with a history of drug dependence. Moreover, patients with mental disorder or cognition disorder, and those who did not cooperate during the study, were excluded.

Drugs and instruments

The experimental drugs and instruments used were remazolam toluenesulfonate manufactured by Jiangsu Heng Rui Pharmaceutical Co. Ltd; (State Food and Drug Administration (SFDA) approval number: H20190034, specification: 36

mg/bottle); ropivacaine hydrochloride injection was produced by AstraZeneca AB Co. Ltd (Imported drug registration certificate number: H20140763 specification: 10 ml：100 mg/piece), and Stimuplex D puncture needle was a product of B Braun, Germany.

Surgical procedure

All patients were given TKA. The venous access of each patient was routinely opened in the operating room, and echocardiogram (ECG), blood pressure (BP), heart rate (HR) and oxygen saturation (SpO_2) of the patients were monitored. In addition, non-invasive continuous blood pressure monitoring procedure was used. Each patient was laid in a supine position, with knee flexion of 90 degrees on the affected limb. The popliteal fossa was scanned with an ultrasonic probe for clear and successive visualisation of the femoral condyle and femoral shaft, as well as the popliteal artery. A Stimuplex D puncture needle was inserted from the outside of the knee joint between the popliteal artery and the femur until the needle tip was 1 cm from the inner edge of the popliteal artery. Then, 10 mL of 0.375 % ropivacaine was injected. The needle was slowly withdrawn until its tip was directly below the popliteal artery, followed by injection of 5 mL of 0.375 % ropivacaine. Again, the needle was withdrawn until the tip was at the lateral edge of the popliteal artery, and 10 mL of 0.375 % ropivacaine was injected while the needle was withdrawn slowly.

Control group was anesthetized with propofol + sufentanil + cis-benzene sulfonic acid atracurium, which specifically involved intravenous injection of propofol (2 mg/kg), sufentanil (0.4 μg/kg) and cis-benzene sulfonic acid atracurium (0.2 mg/kg). If the entropy index was greater than 60, propofol was given at a dose of 1 mg/kg at a time for more than 1 min so as to remedy the anesthesia. The above operations were repeated until the entropy index was less than 60. Mechanical ventilation was performed at inhalation-respiration ratio of 1:2, ventilation frequency of 12 times/min, and tidal volume of 6 mL/min. Anesthesia was maintained in the study group using remazolam toluenesulfonate (0.5 mg/kg/h) plus remifentanil (6 - 12 μg/kg/h), while propofol (0.1 mg/kg/min) and remifentanil (6 – 12 μg/kg/h) were used in the control group. Accurate anesthesia monitoring was performed during the operation, including monitoring of hemodynamic and entropy indices.

Patients in the study group were anesthetized with remazolam toluenesulfonate + sufentanil + cis-benzene sulfonic acid atracurium. This comprised intravenous injection of remazolam toluenesulfonate (0.2 mg/kg), sufentanil (0.4 μg/kg) and cis-benzene sulfonic acid atracurium (0.2 mg/kg). When entropy index was greater than 60, anesthesia was remedied using remazolam toluenesulfonate at a dose of 0.1 mg/kg at a time for more than 1 min. These operations were repeated until the entropy index was less than 60. A laryngeal mask was used on each patient when the anesthesia took effect.

Post-surgery PCA was used for the patients after operation, with sufentanil (2 μg/kg) and ondansetron (8 mg) dissolved in physiological saline to a volume of 100 mL (background dose: 2 mL/h; PCA dose: 2 mL; locking time: 15 min). When the postoperative VAS score was greater than 3, sufentanil (0.1 μg/kg) was injected intravenously to relieve pain.

Evaluation of parameters/indices

Primary outcome

The VAS scores before operation, and at 6, 12 and 24 h post-operation were compared between the two groups [8]. Usually, the VAS score ranges from 0 to 10 points, with higher scores indicating more severe pain. Clinically, VAS scores of 0 - 2 points indicate excellent outcome, 3 - 5 points indicate good outcome, while VAS scores of 6 - 8 and > 8 indicate fair and poor outcomes, respectively. The number of times of pumping with PCA pump after operation, and the frequency of remedial analgesia in the ward within 48 h after operation, were recorded.

Secondary outcome

The two groups were compared with respect to clinical data, quality of anesthesia recovery (spontaneous breathing recovery time, wake up time, and extubation time), and Mini-Mental State Examination (MMSE) scores at 1, 2, and 3 days after operation [9]. The static contraction of quadriceps femoris of the affected side was recorded at 6, 12, 24 and 48 h after operation, and the holding time (limited to 10 sec) and completion time (limited to 10 times) were also recorded. Moreover, incidents of postoperative adverse reactions of patients were recorded.

Statistical analysis

Statistical Packages for the Social Sciences (SPSS 20.0) was used for data analysis, while GraphPad Prism 8 was used for graphics. Independent-sample *t*-test and paired sample *t*-test were used for inter-group and intra-group

comparisons, respectively, while rank sum test and chi-square test were utilized for analysing ranked data (represented by Z) and counting data, respectively. Values of $p < 0.05$ indicated statistically significant differences.

RESULTS

Patients' clinical profile

There were no significant differences in age, gender, body mass index (BMI), past medical history and ASA grade between the two groups ($p > 0.05$). These results are shown in Table 1.

VAS scores before and after operation

The VAS scores of the control group gradually dropped with time, with significant differences in scores at different time points ($p < 0.05$). In contrast, preoperative VAS scores of patients in the study group differed significantly from VAS scores at other time points, but no marked differences were observed among VAS scores at 6, 12 and 24 h after operation ($p > 0.05$). Inter-group comparison revealed that the two groups were similar in VAS scores before operation, but the study group had markedly lower VAS scores than the control group at 6 and 12 h after operation ($p < 0.05$). However, the VAS scores of the two groups at 24 h after operation were similar ($p > 0.05$). These results are shown in Table 2.

Frequency of PCA pumping and analgesia within 24 h post-operation

There was markedly higher frequency of pumping with PCA pump in the control group after operation, and higher frequency of remedial analgesia in ward within 24 h after operation, than the study group ($p < 0.05$; Table 3).

Table 1: Comparison of clinical data

Factor		Control group (n=40)	Study group (n=44)	*P*-value
Age (years)				
	≥ 60	28	35	0.313
	< 60	12	9	
Gender				
	Male	22	26	0.705
	Female	18	18	
BMI				
	≥ 22 kg/m^2	17	22	0.491
	＜22 kg/m^2	23	22	
Past medical history				
	Hypertension	22	28	0.421
	Diabetes mellitus	15	20	0.461
ASA grade				
	Grade I	29	29	0.514
	Grade II	11	15	

Table 2: Comparison of VAS scores at various time points

Group	Before operation	At 6 h after operation	At 12 h after operation	At 24 h after operation
Control (n=40)	4.65±1.05	3.48±0.51*	2.95±0.78*#	2.58±0.50*#&
Study (n=44)	4.41±1.22	2.88±0.81*	2.43±0.50*	2.45±0.50*
t	1.359	3.397	2.945	0.736
P-value	0.537	0.003	0.013	0.916

*$P < 0.05$ *vs.* value before operation; #$p < 0.05$, *vs.* value at 6 h after operation; &$p < 0.05$, *vs.* value at 12 h after operation

Table 3: Comparison of frequencies of PCA pumping and remedial analgesia within 24 h after operation

Group	Frequency of PCA pumping after operation	Frequency of remedial analgesia in ward within 24 h after operation
Control (n=40)	14	11
Study (n=44)	7	4
$\chi 2$	4.073	4.841
P-value	0.044	0.028

Quality of anesthesia resuscitation

There were no significant differences in spontaneous breathing recovery time, recovery time, and extubation time between the two groups ($p > 0.05$). These results are presented in Figure 1.

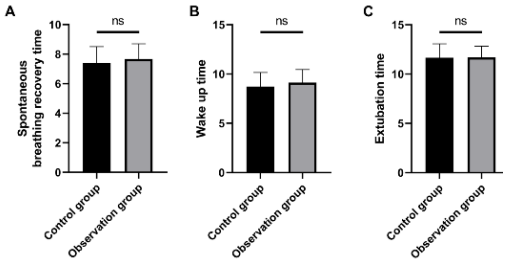

Figure 1: Comparison of quality of anesthesia resuscitation between study (observation) and control groups (min), (A) spontaneous breathing recovery time, (B) wake up time, (C) extubation time

Mental state at different time points

There were gradual decreases in MMSE scores of the two groups at different time points ($p < 0.05$). However, there were no marked differences between the two groups at 1, 2, and 3 days after operation ($p > 0.05$; Table 4).

Static contraction of quadriceps femoris

Intra-group comparison showed that values of static force of quadriceps femoris in the control group at 6, 12 and 24 h after operation differed significantly from the corresponding value at 48 h after operation ($p < 0.05$). However, static force values in the control group at 6, 12 and 24 h after operation were similar. In the study group, the value of static force of quadriceps femoris at 24 h after operation was similar to that at 48 h after operation, but the values of static force at other time points after operation differed significantly ($p < 0.05$). Inter-group comparison showed that the static force of quadriceps femoris at 6 h after operation was similar between the two groups. However, the study group had markedly larger static force than the control group at 12 and 24 h after operation ($p < 0.05$), but the two groups had similar static force values at 48 h after operation ($p > 0.05$). These results are shown in Table 5.

Adverse reactions

The control group had markedly higher total incidence of adverse reactions than the study group ($p < 0.05$, Table 6).

Table 4: Comparison of post-operation MMSE scores

Group	1 day after operation	2 days after operation	3 days after operation
Control (n=40)	11.83±1.11	6.97±1.12*	5.98±1.07*#
Study (n=44)	11.81±1.54	7.06±1.98*	6.18±0.92*#
t	0.067	0.305	0.678
P-value	> 0.05	>0.05	>0.05

*$P < 0.05$, *vs.* value at 1 day after operation; #$p < 0.05$, *vs*. value at 2 days after operation

Table 5: Comparison of static force of quadriceps femoris (kg)

Group	At 6 h after operation	At 12 h after operation	At 24 h after operation	At 48 h after operation
Control (n=40)	2.32±0.85	2.45±0.7	2.69±0.72	3.23±0.64*#&
Study (n=44)	2.12±0.65	3.26±0.78*	3.83±0.5*#	4.07±0.41*#
t	1.359	5.561	7.827	5.767
P-value	0.700	<0.001	<0.001	<0.001

*$P < 0.05$ *vs.* value at 6 h after operation. #$p < 0.05$, *vs.* value at 12 h after operation; &$p < 0.05$, *vs.* value at 24 h after operation

Table 6: Comparison of incidence of adverse reactions

Group	Respiratory depression	Somnolence	Nausea and vomiting	Skin itch	Constipation	Total incidence
Control (n=40)	4	6	4	2	3	19 (47.50)
Study (n=44)	1	2	2	1	2	8 (18.18)
χ^2	2.235	2.658	0.939	0.453	0.326	8.257
P-value	0.135	0.103	0.332	0.501	0.568	0.004

DISCUSSION

Total knee arthroplasty (TKA) is a primary surgical method used for treating knee osteoarthritis. It is a traumatic operation associated with moderate or severe pain which limits physical activity in the patient, thereby seriously compromising their post-surgery recovery [10]. Therefore, there is need to evolve effective anesthesia and analgesia schemes for alleviating TKA-linked postoperative pain in patients while speeding up postoperative rehabilitation. The simplified adductor canal block is a peripheral nerve block which relieves postoperative pain in patients to a certain extent. However, this technique provides only pain relief in the frontal and medial parts of the knee joint, it hinders full extension of the knee joint and prolongs the time patients stay in bed [11].

The use of IPACK block scheme was recently proposed by researchers [12]. It blocks the deep nerve of the knee joint via anesthesia infiltration of the space between popliteal artery and posterior capsule of knee joint [13]. It has been reported that IPACK selectively blocks the terminal sensory branches in the back of knee joint without involving the motor branches of tibia and peroneal nerve, thereby relieving pain in patients without affecting muscle strength [14]. Currently, propofol is the most frequently used anesthesia in IPACK regimen [15]. Propofol takes effect quickly and it has strong controllability. Thus, it is often adopted as an auxiliary sedative for spinal anesthesia. However, propofol injection is painful, and it often triggers respiratory depression [16].

The effect of remazolam toluenesulfonate, a benzodiazepine anesthetic sedative, is not prolonged by continuous pumping because it binds rapidly to its receptor, has a short half-life, and its metabolism is independent of P450 system [17]. A study has shown that, in contrast to midazolam and propofol which are frequently used as anaesthetic sedatives, remazolam toluenesulfonate has advantages of quick effect, low influence on respiratory cycle, quick metabolism, inactive metabolites, weak interaction with drugs, and rapid effect-reversal using flumazenil [18]. However, prior to the present study, it was not clear whether remazolam toluenesulfonate could replace propofol in IPACK.

The present study compared the efficacies of remazolam toluenesulfonate and propofol in IPACK for patients undergoing TKA. The results showed that VAS scores of the study group dropped markedly after operation, without marked differences in VAS scores at 6, 12 and 24 h after operation. Although the VAS scores of the control group at these time points were different, VAS scores were similar between the two groups at 24 h after operation. Moreover, there was lower frequency of PCA pumping after operation, and lower frequency of remedial analgesia in ward within 48 h after operation, relative to control group.

There was significantly better recovery of quadriceps femoris muscle strength in the study group than in the control group. The results imply the superior potential of remazolam toluenesulfonate in alleviating postoperative pain, reducing postoperative analgesia times, and improving postoperative rehabilitation.

There were no marked differences in spontaneous breathing recovery time, wake up time, extubation time, and MMSE scores between the two groups. This suggests that remazolam toluenesulfonate did not affect the quality of anesthesia recovery and mental state of patients. However, in a previous study [19], patients sedated with remazolam toluenesulfonate had significantly shorter recovery time after operation than those sedated with midazolam and propofol.

This is at variance with the results obtained in the present study. The difference may be due to differences in anesthetic schemes used. Moreover, in the present study, the two groups did not differ markedly in postoperative complications, although the control group had higher total incidence adverse events, indicating that remazolam toluenesulfonate did not increase the incidence of postoperative adverse reactions in patients undergoing TKA.

This study has revealed that the combination of remazolam toluenesulfonate and IPACK relieved postoperative pain, reduced the frequency of PCA pumping after operation, and frequency of remedial analgesia within 48 after operation, without affecting the quality of recovery and neurological function of patients.

Limitations of the study

Firstly, being a retrospective study, the results may be biased, in contrast to a randomized controlled experiment. Secondly, due to the short time of drug listing in China, the research sample sizes were limited. Therefore, the sample size will be increased in future investigations that will be randomized controlled studies for validating the conclusions arrived at in this study.

CONCLUSION

Remazolam toluenesulfonate - IPACK combination substantially alleviates pain in elderly patients undergoing total knee arthroplasty, and also improves their sedation level, without increasing cognitive dysfunction. Thus, the combination treatment will be beneficial to postoperative recovery, but further clinical trials are recommended.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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