Comparative Effect of Intravenous Ketamine and Tramadol on Hemodynamic Parameters, Pain, Sedation, and Postoperative Nausea and Vomiting in Patients Undergoing Urological Surgery Under Spinal Anesthesia: A Triple-Blind Randomized Clinical Trial

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Abstract

Background: Spinal anesthesia is widely used in urological surgeries but is often associated with hemodynamic instability, insufficient sedation, and postoperative nausea and vomiting (PONV). While ketamine and tramadol have been employed as adjuncts, their comparative effects on perioperative parameters remain underexplored. This study aimed to compare the efficacy of intravenous ketamine and tramadol in modulating hemodynamic stability, sedation, pain, and PONV in patients undergoing urological surgery under spinal anesthesia.

Methods: In this triple-blind randomized clinical trial, 90 patients undergoing transurethral or ureteroscopic urological surgeries under spinal anesthesia were randomly allocated into 3 equal groups: ketamine (0.5 mg/kg IV), tramadol (0.5 mg/kg IV), or saline. Hemodynamic parameters, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO_2), were recorded at multiple intraoperative and postoperative time points. Secondary outcomes included pain scores, sedation levels, and incidence of PONV. The data were entered into SPSS software, Version 21, and analyzed using the chi-square test, independent sample t-test, and repeated-measures analysis of variance with post-hoc Bonferroni tests.

Results: The study population exhibited demographic consistency. Ketamine demonstrated significantly superior hemodynamic stability compared to tramadol and saline, with less reduction in SBP, DBP, and MAP over time (MAP: $P < 0.001$, $\eta^2 = 0.33$). The heart rate was also more stable in the ketamine group ($P < 0.001$, $\eta^2 = 0.11$). The ketamine group showed the highest sedation scores (mean increase: -0.91, $P \leq 0.001$) and the lowest incidence of PONV (3.3%) compared to tramadol (16.7%) and saline (10%) ($P = 0.017$, $\varphi = 0.34$). Pain scores showed no significant differences among groups. No serious adverse effects, including hallucinations or hypersensitivity reactions, were reported.

Conclusion: Intravenous ketamine significantly enhances hemodynamic stability, increases sedation, and reduces PONV when used as an adjunct to spinal anesthesia in urological surgeries. These findings support the clinical use of ketamine to optimize perioperative outcomes and patient safety. These findings possess external validity and may be extrapolated to broader populations undergoing urological procedures under spinal anesthesia.

Keywords: Spinal Anesthesia, Ketamine, Tramadol, Urological Surgery, Hemodynamic Stability, Sedation, PONV

Cite this article as: Sangi S, Mesbah Kiaei M, Sedigh Maroufi S, Aligholizadeh M,　Rajabzadeh R, AmouzegarZavareh SMR, Mohaghegh

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↑*What is "already known" in this topic:*
Before this study, it was known that spinal anesthesia in urological surgeries can cause hemodynamic instability, pain, sedation issues, and postoperative nausea and vomiting (PONV). Ketamine and tramadol have been used as adjuncts; however, comparative evidence is limited.

→*What this article adds:*
This study demonstrated that intravenous ketamine provides superior hemodynamic stability, increased sedation, and reduced PONV compared to tramadol and saline, supporting its use as an effective adjunct to spinal anesthesia in urological surgeries.

Introduction

Urinary tract diseases are among the most prevalent medical conditions, leading to a high frequency of urological surgeries worldwide (1, 2). Spinal anesthesia is a widely accepted and reliable anesthetic method for such procedures, offering numerous benefits, including effective pain relief and reduced systemic complications. However, spinal anesthesia is not without challenges; it often causes sympathetic blockade, leading to vasodilation and parasympathetic dominance, which in turn can result in hemodynamic instability, including hypotension and bradycardia (3, 4). Additionally, patients undergoing spinal anesthesia frequently experience postoperative nausea and vomiting (PONV), pain, and sedation-related complications, all of which can adversely affect recovery and overall patient satisfaction (5-7). The hemodynamic instability associated with spinal anesthesia presents a particularly significant challenge during urological surgeries such as transurethral prostate resection and ureteroscopic stone fragmentation (8, 9). Compounding this issue is the prevalence of comorbidities among patients undergoing urological procedures, with hypertension (56.3%) and diabetes (16.2%) being common (10). Pain following urological surgeries is another critical concern and negatively impacts physical and mental health, causing issues such as sleep disturbances, anxiety, and diminished quality of life (11, 12). Effective management of intraoperative hemodynamic fluctuations and postoperative complications is thus essential for optimizing patient outcomes. Nausea and vomiting in the postoperative phase continue to represent some of the most prevalent adverse effects associated with spinal anesthesia, with significant implications for patient recovery and satisfaction (13). Pharmacological interventions are critical in addressing these challenges. Adjunctive agents to spinal anesthesia have been explored to minimize hemodynamic instability, reduce pain, and prevent PONV (14). Despite developments, there is still little data comparing the effects of various adjuncts, especially when it comes to urological procedures. Ketamine increases sympathetic outflow and inhibits norepinephrine absorption by antagonizing NMDA and influencing noradrenergic and serotonergic pathways.

It also potentiates GABAergic inhibition, promotes dopamine release, acts as a weak opioid receptor agonist, and exerts anti-inflammatory effects by suppressing cytokine production and neutrophil adhesion (15). In contrast, tramadol, a synthetic opioid with dual mechanisms of action, is commonly used for moderate to severe pain management. Tramadol has also demonstrated efficacy in reducing PONV because of its limited respiratory depressant effects compared to traditional opioids, although its hemodynamic effects in the setting of spinal anesthesia require further elucidation (16). Intravenous sedation is increasingly recognized for its role in improving perioperative outcomes during urological procedures, with evidence supporting its safety and efficacy in reducing complications (17). Despite these advances, direct comparative evaluations of intravenous ketamine and tramadol as preemptive adjuncts to spinal anesthesia are sparse. This study addresses this gap by evaluating the prophylactic administration of ketamine and tramadol before surgical incision. It assesses their impact on primary outcomes such as hemodynamic parameters, including heart rate (HR) and mean blood pressure (MBP), and secondary outcomes such as pain, sedation, and PONV. The findings aim to contribute to evidence-based improvements in perioperative care for urological surgeries. This study seeks to advance the understanding of optimal anesthetic adjuncts and contribute to evidence-based improvements in perioperative care.

Methods

Design and Settings

This study was designed as a triple-blind, randomized controlled clinical trial comprising 1 control arm and 2 experimental groups. Ethical approval was granted by the institutional review board under protocol number IR.IUMS.REC.1402.879, and the study was prospectively registered with the Iranian Registry of Clinical Trials (IRCT20231021059799N1). The trial spanned 9 months at the operating theaters and postoperative recovery units of Shahid Hasheminejad Teaching and Medical Center, affiliated with Iran University of Medical Sciences.

Participant Eligibility

To ensure the integrity and safety of the trial, stringent eligibility and exclusion criteria were established. Patients aged 18 to 80 years, classified as ASA I–III, and scheduled for transurethral prostate resection and ureteroscopic stone fragmentation were eligible for inclusion. Participants were excluded if they exhibited contraindications to spinal anesthesia, localized infection at the intended injection site, or a body mass index exceeding 38 kg/m². The use of beta-blockers, poorly controlled diabetes mellitus, valvular heart pathology, or diagnosed psychiatric conditions, such as stroke. Individuals with known hypersensitivity to ketamine or tramadol, a history of substance abuse (including drugs or alcohol), or a body temperature exceeding 37.5°C, massive intraoperative bleeding, underwent surgical procedures lasting longer than 3 hours, or had a documented history of severe PONV associated with prior urological interventions.

Sample Size

The sample size was determined using G*Power 3.1 software, employing a confidence interval of 95% and a statistical power of 80%. The calculation assumed a mean difference between groups (μ1 - μ2) of 1.7, with an estimated standard deviation (σ) of 0.9, and accounted for a 20% attrition rate. To accommodate potential participant

dropout, 30 individuals were assigned to each study arm, resulting in a total of 90 participants. The primary endpoint for this calculation was the variation in mean arterial pressure (MAP) across the 3 groups. The standard deviation estimate was derived from data reported in prior studies (8).

Randomization

Qualified patients were selected from the patient cohort and randomly distributed across 3 study arms using a block randomization approach. The randomization utilized sequences of 6 blocks (eg, ACBBAC, CBABCA, etc), created through Microsoft Excel. To maintain blinding, allocation codes were placed in sealed, opaque envelopes and handled by an independent epidemiologist.

Blinding Protocol

To implement a robust blinding strategy, participants were kept uninformed about the specific medications they were administered. Similarly, research assistants responsible for data collection and assessments, as well as the statistician conducting the data analysis, were unaware of the group allocations. Furthermore, healthcare providers, including clinicians and nursing staff in the operating and recovery areas, were also blinded to the group assignments. This trial adopted a triple-blind methodology, ensuring that the participants, data collectors/evaluators, and the statistical analyst remained unaware of the treatment allocations throughout the study.

Interventions

After the administration of spinal anesthesia, participants were intravenously administered one of the following treatments: ketamine at a dose of 0.5 mg/kg (ketamine group), tramadol at a dose of 0.5 mg/kg (tramadol group), or an equivalent volume of saline solution (control group). The interventions were initiated only after an independent anesthesiologist verified the adequacy of spinal anesthesia. The timing of the treatment administration coincided with the confirmation of effective spinal anesthesia.

Study Procedures

Before the commencement of the trial, a comprehensive training session was conducted to outline the study's objectives, methodology, medication coding, participant blinding, and overall study blinding protocols. This ensured that interactions between participants and anesthesiologists did not jeopardize the randomization or blinding processes. All participants provided written informed consent. Preoperatively, patients received 5 to 6 mL/kg of normal saline, with intraoperative fluid administration maintained at 7 to 8 mL/kg/hour. Spinal anesthesia was delivered using 2 to 3 mL of 0.5% bupivacaine through a Quincke needle inserted at the L3 to L5 vertebral interspace. Supplemental oxygen was provided at a flow rate of 6 L/min via a face mask. The ambient temperature in the operating and recovery rooms was maintained between 22°C and 24°C. Vital parameters, including systolic blood pressure (SBP), diastolic blood pressure, MAP, HR, and SpO$_2$, were monitored and recorded before surgery and at regular intervals during the surgical procedure and postoperative recovery phase.

Outcome Measure

The primary endpoints of the study encompassed variations in systolic and diastolic blood pressure, HR, MAP, and SpO$_2$. Secondary endpoints included evaluations of postoperative pain, PONV, and sedation levels. Pain severity was quantified using a numerical rating scale ranging from 0 to 10, where 0 denoted "no pain" and 10 indicated "the most severe pain imaginable." The test-retest reliability of this scale was determined to be 0.92. The intensity of postoperative nausea and vomiting was assessed using a numerical rating scale from 0 to 10, with higher values reflecting greater severity of symptoms. Sedation was evaluated using a modified Ramsay Sedation Scale, categorized as follows: 1 = fully alert and anxious; 2 = calm and cooperative; 3 = asleep but arousable with verbal commands; 4 = asleep, arousable with mild stimulation, and exhibiting a strong response to painful stimuli; 5 = sluggish response to painful stimuli; and 6 = no response to painful stimuli (18). The Ramsey Sedation Scale is the most widely used in clinical practice today and is a valid Scale (19, 20). Safety outcomes included the incidence of adverse effects such as hallucinations, drug-related hypersensitivity reactions, and other side effects attributable to ketamine or tramadol. These outcomes were assessed using a standardized adverse event reporting form

Data Collection and Instrument Reliability

Information was gathered using a uniform template that recorded demographic details, hemodynamic metrics, and postoperative results. Each participant was assigned a distinct identifier displayed at the top of their respective form. The reliability of the data collection tool was reassessed through the intraclass correlation coefficient method, applied to 20 excluded participants, yielding a correlation coefficient of 0.867.

Statistical Methods

Data analyses were conducted using SPSS software, Version 21.0. The distribution of continuous variables was evaluated for normality with the Kolmogorov-Smirnov test. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were computed to characterize the demographic and clinical profiles of the participants. For group comparisons involving categorical variables, the chi-square test was employed, with the Fisher exact test used when the expected cell frequencies were <5. Between-group comparisons of continuous variables at single time points were conducted using 1-way analysis of variance (ANOVA). Repeated measures ANOVA was employed to examine within- and between-group differences over time in hemodynamic parameters (SBP, DBP, MAP, HR, SpO$_2$). Post hoc Bonferroni tests were used for pairwise comparisons when overall group-time interactions were statistically significant. Effect sizes were reported as partial eta squared (η^2) for ANOVA-

based tests and phi coefficient (φ) for chi-square tests to quantify the magnitude of observed effects. $P < 0.05$ was considered statistically significant.

Results

A total of 90 patients were randomized into 3 groups: ketamine, tramadol, and control, and all participants completed the study. The participant flow throughout the trial is illustrated in Figure 1. Measurements were conducted preoperatively and at intervals during surgery and recovery. No adverse effects or unintended consequences of the interventions were reported. The mean age of participants in the intervention and control groups was 48.06 years (SD, 13.98 [95% CI, 45.01- 51.11]) and 43.77 years (SD, 14.16 [95% CI, 40.55-46.99]), respectively. Most participants were men, comprising 55% of the intervention group and 53.3% of the control group. Preintervention pain intensity showed no significant differences between groups (F = 1.88, $P = 0.17$, $\eta^2 = 0.021$). Similarly, repeated-measures ANOVA demonstrated no significant difference in pain intensity trends among the groups over time (F = 1.16, $P = 0.28$, $\eta^2 = 0.014$). These findings indicate comparable efficacy of the interventions regarding pain management across the study duration. Demographic variables, including age, sex, marital status, education level, ASA classification, and BMI, were distributed homogeneously across the groups ($P > 0.05$) (Table 1). The distribution of intraoperative characteristics, such as the kind and length of operation, and underlying diseases, such as diabetes and hypertension, also did not significantly differ between groups ($P > 0.05$), suggesting that randomization was successful.

The repeated measures ANOVA revealed statistically significant time-group interactions for SBP, diastolic blood pressure (DBP), MAP, and HR, indicating differential trends among groups across time points. Specifically, SBP exhibited a significant within-subject effect $P < 0.001$, partial $\eta^2 = 0.30$), with post hoc comparisons identifying a significantly higher SBP at 30 minutes in the ketamine group compared to saline ($P = 0.015$), reflecting superior cardiovascular stability. Similarly, DBP also demonstrated significant within-group variation ($P < 0.001$, partial $\eta^2 = 0.30$), particularly marked in the ketamine group, which maintained more consistent pressure profiles. MAP trends mirrored these findings, with a notable time effect ($P < 0.001$, partial $\eta^2 = 0.33$), highlighting
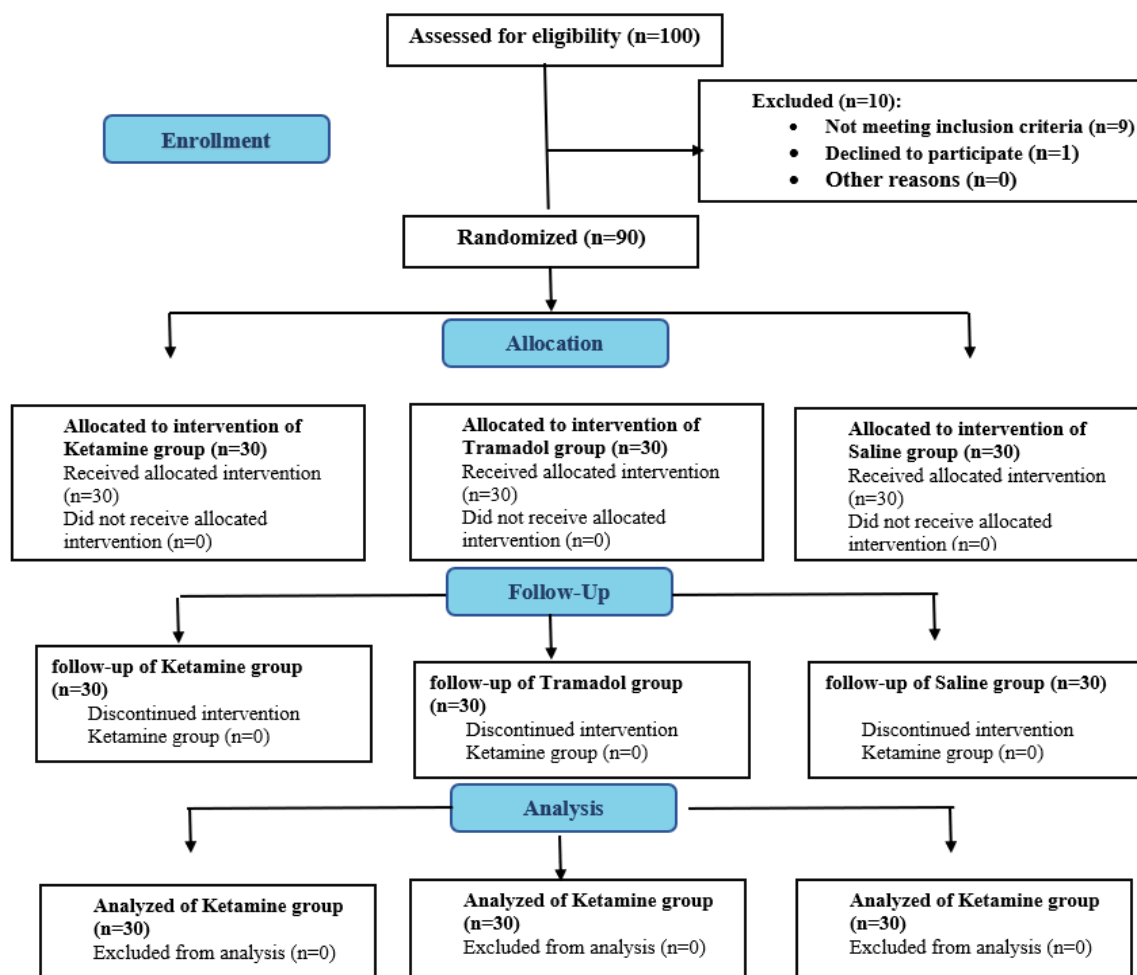

Figure 1. Flow diagram of participants in this study

Table 1. Distribution and Comparative Analysis of Demographic and Operating Characteristics Across Study Groups

Variable	Saline (n, %)	Tramadol (n, %)	Ketamine (n, %)	X²	P-value
Age				7.74	0.258
18-40 years	11 (36.7%)	5 (16.7%)	10 (33.3%)		
41-50 years	8 (26.7%)	7 (23.3%)	8 (26.7%)		
51-60 years	8 (26.7%)	7 (23.3%)	5 (16.7%)		
61-80 years	3 (10.0%)	11 (36.7%)	7 (23.3%)		
Gender				0.09	0.956
Male	16 (53.3%)	17 (56.7%)	16 (53.3%)		
Female	14 (46.7%)	13 (43.3%)	14 (46.7%)		
Marital Status				2.06	0.358
Single	8 (26.7%)	4 (13.3%)	8 (26.7%)		
Married	22 (73.3%)	26 (86.7%)	22 (73.3%)		
University	9 (30.0%)	7 (23.3%)	7 (23.3%)		
Hypertension				0.37	0.832
No	17 (56.7%)	19 (63.3%)	17 (56.7%)		
Yes	13 (43.3%)	11 (36.7%)	13 (43.3%)		
Diabetes				0.42	0.812
No	25 (83.3%)	24 (80.0%)	23 (76.7%)		
Yes	5 (16.7%)	6 (20.0%)	7 (23.3%)		
Addiction				Fisher	0.288*
No	28 (93.3%)	23 (76.7%)	25 (83.3%)		
Yes	2 (6.7%)	7 (23.3%)	5 (16.7%)		
ASA class				0.89	0.956
1	16 (53.3%)	15 (50.0%)	16 (53.3%)		
2	13 (43.3%)	9 (30.0%)	10 (33.3%)		
3	1 (3.3%)	6 (20.0%)	4 (13.3%)		
Type of Surgery				0.27	0.875
TUL	16 (53.3%)	14 (46.7%)	15 (50.0%)		
TURP	14 (46.7%)	16 (53.3%)	15 (50.0%)		

a more stable perfusion pressure in the ketamine group over the perioperative course. In contrast, tramadol and saline groups exhibited more pronounced hypotensive episodes, especially at 30 minutes postspinal anesthesia (Figure 2). HR analysis confirmed a significant interaction $P < 0.001$, partial $\eta^2 = 0.11$), where ketamine induced a modest yet clinically stabilizing increase in HR during the intraoperative and early recovery phases, potentially reflecting its sympathomimetic properties. Although SpO_2 values were generally stable across all groups, a small but statistically significant group-time effect was observed P

< 0.001, partial $\eta^2 = 0.08$), primarily attributable to transient differences at 30 minutes, with slightly lower oxygen saturation (SPO_2) in the tramadol group compared to saline (Table 2).

Postanesthesia sedation scores increased significantly in all groups ($P \leq 0.01$). The ketamine group exhibited the highest sedation scores, with a mean increase of -0.91 points ($P \leq 0.001$), compared to -1.24 in the tramadol group and -0.74 in the control group (Table 3).

Incidence rates of PONV differed significantly across groups ($P = 0.017$). The ketamine group reported the low-
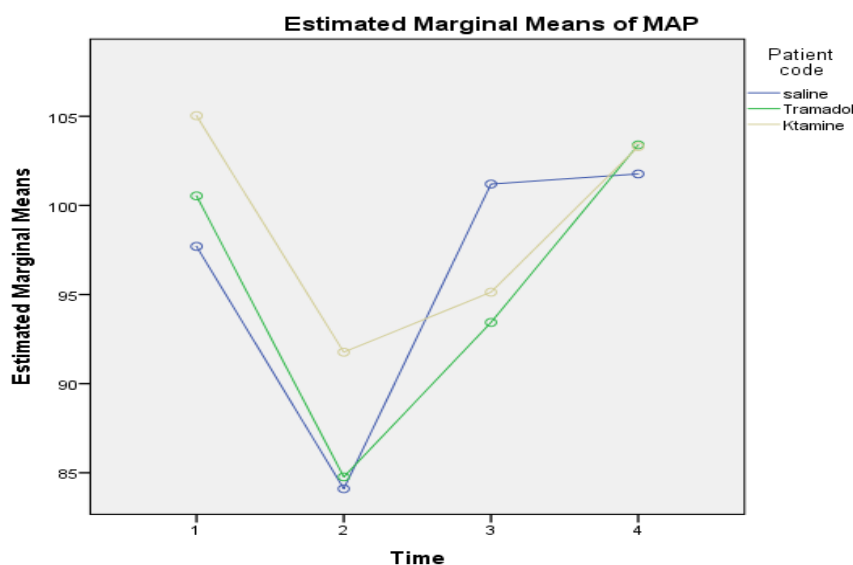

Figure 2. Comparison of hemodynamic parameters (mean arterial blood pressure) in study groups

est prevalence of PONV (3.3%), followed by the control group (10.0%) and the tramadol group (16.7%), with a moderate effect size (ϕ = 0.34). There were no significant differences in the incidence of hallucinations among the groups (*P* = 0.264) (Table 4). No allergic responses were noted across any of the study groups. The occurrence of hallucinations was most frequent in the ketamine group (20%), followed by the tramadol group (6.7%), and the lowest in the control group (3.3%) (*P* = 0.264). No other significant safety concerns were reported during the study period.

Discussion

Spinal anesthesia is widely preferred for its proven benefits, superior postoperative pain control, and reduced respiratory complications. However, it may cause adverse effects such as hypotension, nausea, and vomiting, and can lead to a reduction in systemic vascular resistance (SVR), resulting in hypotension (21, 22). To mitigate this risk, administering a lower dose of local anesthetics has been suggested (23). However, the use of small doses may limit the extent of the block and result in inadequate sensory blockade (24). Although controversial, some studies have shown the effectiveness of fluid therapy in reducing the incidence of hypotension during spinal anesthesia, but

Table 2. Group Comparisons in Terms of Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure, Heart Rate, and Oxygen Saturation at Different Time Intervals

Parameter	Time Point	Saline (Mean ± SD)	Tramadol (Mean ± SD)	Ketamine (Mean ± SD)	F (df1, df2)	*P*-value	Partial η²
SBP (mmHg)	5 min	128.73 ± 18.07	131.03 ± 18.62	138.57 ± 17.77	$F_{(2, 87)} = 2.41$	0.096	—
	30 min	111.23 ± 14.96	113.63 ± 15.05	123.10 ± 17.78	$F_{(2, 87)} = 4.62$	0.012	—
	Recovery start	132.13 ± 18.17	123.27 ± 23.56	125.87 ± 21.14	$F_{(2, 87)} = 1.40$	0.251	—
	Recovery end	131.70 ± 13.82	134.00 ± 18.23	134.80 ± 16.59	$F_{(2, 87)} = 0.29$	0.748	—
					$F_{(2.51, 218.58)} = 37.37$	<0.001	0.30
DBP (mmHg)	5 min	82.73 ± 13.01	85.10 ± 16.71	90.23 ± 11.33	$F_{(2, 87)} = 2.29$	0.107	—
	30 min	70.33 ± 12.66	71.63 ± 15.09	84.67 ± 11.57	$F_{(2, 87)} = 2.82$	0.065	—
	Recovery start	84.67 ± 11.57	78.73 ± 17.97	79.37 ± 12.61	$F_{(2, 87)} = 1.43$	0.244	—
	Recovery end	85.73 ± 11.75	87.07 ± 13.28	86.67 ± 11.36	$F_{(2, 87)} = 0.095$	0.909	—
					$F_{(2.68, 233.32)} = 36.51$	< 0.001	0.30
MAP (mmHg)	5 min	97.70 ± 14.28	100.53 ± 17.53	105.03 ± 13.35	$F_{(2, 87)} = 1.79$	0.174	—
	30 min	84.10 ± 13.44	84.77 ± 15.44	91.77 ± 14.55	$F_{(2, 87)} = 2.57$	0.082	—
	Recovery start	101.20 ± 14.60	93.43 ± 20.08	95.13 ± 16.21	$F_{(2, 57.12)} = 1.87$	0.163	—
	Recovery end	101.77 ± 11.10	103.40 ± 16.33	103.30 ± 13.22	$F_{(2, 56.59)} = 0.16$	0.852	—
					$F_{(2.59, 225.59)} = 42.11$	< 0.001	0.33
HR (bpm)	5 min	77.77 ± 10.86	82.43 ± 15.17	89.80 ± 13.36	$F_{(2, 87)} = 6.29$	0.003	—
	30 min	78.47 ± 13.06	72.93 ± 10.65	81.70 ± 13.65	$F_{(2, 87)} = 3.76$	0.027	—
	Recovery start	83.53 ± 12.97	72.07 ± 8.73	79.03 ± 11.85	$F_{(2, 87)} = 7.81$	0.001	—
	Recovery end	81.50 ± 10.77	76.17 ± 10.73	80.90 ± 11.15	$F_{(2, 87)} = 2.16$	0.121	—
					$F_{(2.44, 212.34)} = 10.61$	< 0.001	0.11
SpO₂ (%)	5 min	96.43 ± 1.78	96.17 ± 2.78	96.43 ± 1.43	$F_{(2, 87)} = 0.17$	0.848	—
	30 min	97.17 ± 1.42	95.80 ± 1.94	96.47 ± 1.57	$F_{(2, 87)} = 5.11$	0.008	—
	Recovery start	96.83 ± 1.36	96.50 ± 1.54	97.07 ± 1.50	$F_{(2, 87)} = 1.12$	0.332	—
	Recovery end	97.43 ± 1.17	96.77 ± 1.43	97.07 ± 1.46	$F_{(2, 87)} = 1.81$	0.169	—

Table 3. Comparison Among the Groups in Terms of Sedation Score Before and After Anesthesia

	Before anesthesia Mean (SD)	After anesthesia Mean (SD)	The mean difference	*P*-value
Ketamine	1.18 (0.39)	2.36 (0.89)	-0.91	<0.001
Tramadol	1.12 (0.38)	2.09 (0.63)	-1.24	<0.001
Control	1.24 (0.43)	1.98 (0.4)	-0.74	<0.001

Table 4. Comparison Among the Groups in Terms of Hallucinations, Nausea, and Vomiting During Surgery and Pethidine Consumption.

Hallucination during surgery	Tramadol	Ketamine	Control	χ²	*P* value
Yes	2	6	1	2.77	0.264
No	28	24	29		
Nausea and vomiting during surgery	Tramadol	Ketamine	Control	χ²	P value
Yes	5	1	3	8.21	0.017
No	25	29	27		

these interventions carry the potential risk of complications, such as pulmonary edema (25, 26). Therefore, a drug or premedication is needed to maintain hemodynamics. This study offers a comparative analysis of intravenous ketamine and tramadol as adjuncts to spinal anesthesia in patients undergoing urological surgeries, with a focus on hemodynamic parameters, pain control, sedation, and PONV. The findings underscore the distinct advantages of ketamine over tramadol and saline, particularly in maintaining hemodynamic stability, improving sedation levels, and significantly reducing PONV.

In this study, ketamine demonstrated superior hemodynamic stability, evidenced by a smaller reduction in MAP postanesthesia compared to tramadol and the control group. The sympathomimetic properties of ketamine modulate noradrenergic and serotonergic activity in the locus coeruleus, enhancing sympathetic outflow, which counteracts the vasodilation and bradycardia induced by spinal anesthesia, likely explains this finding (27). These results are consistent with the findings of several studies (16). Conversely, tramadol was associated with the greatest reductions in systolic and diastolic pressures, emphasizing its comparatively limited role in stabilizing hemodynamics under these conditions. This observation contrasts with the findings of Mahdi et al, who reported that tramadol enhances hemodynamic stability compared to bupivacaine alone (28). This variation in results may be due to differences in the administration methods of ketamine and tramadol, as they were administered epidurally and at different dosages.

Postoperative pain intensity scores did not show statistically significant differences between the groups, suggesting that both ketamine and tramadol were similarly effective in managing pain. However, this result is inconsistent with the study by Naghipour et al, which demonstrated the superiority of ketamine over tramadol for pain control, along with fewer adverse effects (29). Additionally, Raheem et al demonstrated that epidural ketamine is more effective than epidural tramadol in pain reduction ($P < 0.05$) (30). Additionally, Aboelsuod et al demonstrated that preoperative intravenous infusion of ketamine significantly lowered postoperative pain levels compared to a placebo in cesarean section patients under spinal anesthesia ($P < 0.05$) (31). In our study, ketamine also reduced postoperative pain in patients who did not receive any analgesic or premedication, but this difference was not statistically significant and could be due to differences in the dose of ketamine or tezamadol, the type of surgery, and the amount and duration of spinal anesthesia.

Regarding sedation, ketamine resulted in significantly higher sedation scores compared to tramadol and saline. This observation aligns with ketamine's mechanism of action as an NMDA receptor antagonist, which enhances its sedative effects (32). These findings are consistent with Mahdi et al, who reported higher sedation levels with ketamine than tramadol ($P < 0.001$) (28). However, our results differ from those of Raheem et al, who observed greater sedation scores in the epidural tramadol group compared to the ketamine group (0.71 ± 1.44 vs 0 ± 1, $P < 0.004$) (30). The mechanism of epidural is quite different

from spinal, and in that study, the dose of ketamine was 0.25 mg/kg, which is different from our prescribed dose.

A significant reduction in PONV was observed in the ketamine group, further supporting its utility as an anesthetic adjunct. This effect may stem from ketamine's anti-inflammatory and anti-hyperalgesic properties, which potentially reduce the central sensitization contributing to PONV. Ketamine promotes dopamine release and has anti-inflammatory effects by suppressing cytokine production and neutrophil adhesion (33). By contrast, the tramadol group exhibited the highest incidence of PONV, highlighting the need for caution when using tramadol in patients predisposed to nausea and vomiting. These findings are in agreement with Raheem et al, who reported a lower incidence of PONV with epidural ketamine compared to epidural tramadol ($P = 0.049$) (30). Additionally, the study by Lodhi et al demonstrated that intraoperative infusion of ketamine and dexmedetomidine during general anesthesia resulted in a lower incidence of PONV compared to the combination of fentanyl and dexmedetomidine (34). However, Burimsittichai et al observed a higher incidence of PONV in the ketamine group, although the difference was not statistically significant compared to the tramadol or placebo groups (35). Thus, this study demonstrates that premedication with intravenous ketamine at a dose of 0.5 mg/kg effectively reduces excessive sympathetic block while maintaining hemodynamic stability. Additionally, ketamine minimizes side effects such as nausea and vomiting, enhances sedation, and improves the overall quality of anesthesia.

Study Limitations
Restricted and challenging access to intravenous tramadol was overcome through dedicated efforts by the research team to ensure a sufficient supply. Hesitation from some participants to enroll in the study was addressed by the researcher offering thorough and transparent explanations to secure their informed consent. The study was conducted on 2 types of surgeries (urological), and the findings may not be directly applicable to other surgical fields. The relatively small sample size may also restrict the applicability of results to larger populations. Finally, unmeasured confounders, such as variations in surgical techniques or preoperative anxiety, may have influenced the outcomes. Despite these limitations, the study provides valuable evidence supporting the use of ketamine in spinal anesthesia.

Recommendations for Future Researches
Subsequent investigations should explore the impact of varying dosages of these medications across different surgical procedures. It would be beneficial to assess the long-term adverse effects and potential interactions with other medicines. Researchers are urged to carry out research with more diverse and sizable populations, including people with a range of demographics and medical issues.

Conclusion
This study highlights ketamine's advantages over tra-

madol and saline as an adjunct to spinal anesthesia in urological surgeries. Ketamine's ability to maintain hemodynamic stability, enhance sedation, and reduce PONV offers significant clinical benefits, particularly in managing patients with comorbidities or high susceptibility to intraoperative complications. These findings underscore the importance of tailoring anesthetic adjuncts to individual patient profiles and surgical contexts to optimize perioperative outcomes. The findings of this investigation may be applied to individuals undergoing urological procedures under spinal anesthesia. Therefore, drug selection should be based on consideration of the side effects of the drugs, patient condition, and physician preferences.

Authors' Contributions

S.S. conceived the study, supervised the project, and led the manuscript drafting. M.A. and M.M.K. contributed to the study design, data collection, and clinical implementation. R.R. provided methodological and statistical consultation and assisted with data interpretation. P.M. supported participant recruitment, randomization procedures, and ethics compliance. M.R.M.D. contributed to data analysis and manuscript revision. S.S.M. participated in the literature review and manuscript formatting. S.M.R.A.Z. Critically reviewed the clinical content and helped refine the discussion. All authors reviewed and approved the final version of the manuscript.

Ethical Considerations

The present study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Iran University of Medical Sciences (Approval Code: IR.IUMS.REC.1402.879), and the trial was prospectively registered in the Iranian Registry of Clinical Trials (Registration Code: IRCT20231021059799N1). Before enrollment, written informed consent was obtained from all participants after providing them with comprehensive information regarding the study objectives, procedures, potential risks, and benefits. Participants were informed of their right to withdraw from the study at any stage without any impact on their medical care. To ensure confidentiality, all personal identifiers were removed and data were anonymized, with access restricted solely to the research team.

Acknowledgment

Conflict of Interests

The authors declare that they have no competing interests.

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