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ORIGINAL RESEARCH AMBULATORY ANESTHESIA

Dexmedetomidine-propofol versus ketamine-propofol for sedation of cancer patients undergoing computerized tomography guided bone biopsy: a randomized double-blind trial

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ABSTRACT

Background & Objective: Patients suffering from malignancy, often need to undergo computed tomography (CT) for evaluation or for CT-guided bone biopsy. They are shifted to the radio-diagnostic suite and require sedation and analgesia during this procedure. We compared the efficacy and safety of combining dexmedetomidine (DEX) or ketamine with propofol for better sedation among these patients undergoing CT-guided bone biopsy.

Methodology: This randomized, double-blind study was done on 60 adult cancer patients undergoing CT-guided bone biopsy. Patients were randomized into two equal groups. Group D received DEX 1 µg/kg (over 10 min) + propofol 2.5 mg/kg intravenous (IV). It was followed by DEX 0.5 µg/kg/h + propofol 2.5 mg/kg/h infusion. Group K received ketamine 1 mg/kg + propofol 2.5 mg/kg IV, followed by ketamine 0.25 mg/kg/h + propofol 2.5 mg/kg/h infusion.

Results: The total intra-procedure propofol consumption was significantly decreased in Group D than in Group K ($P < 0.05$). The visual analog scale score at 15 min and 30 min post-procedure, number of patients requiring morphine and paracetamol within one hour of procedure and the recovery times were significantly decreased in Group D than in Group K ($P < 0.05$). Mean arterial pressure (MAP) and heart rate (HR) measurements at 10 min, 20 min, end of the procedure, and 15 min, 30 min post-procedure was significantly decreased in Group D than in Group K ($P < 0.05$). Adverse events, e.g., postoperative nausea and vomiting, hypotension, and bradycardia, were comparable.

Conclusion: DEX-propofol combination had superior sedation efficacy as noted through lower pain scores, intraprocedural propofol or postprocedural morphine and paracetamol consumption, and the shorter recovery time during CT-guided bone biopsy compared to ketamine-propofol combination. However, ketamine-propofol combination exhibited superior hemodynamic stability, as shown by more consistent HR and MAP.

Keywords: Dexmedetomidine; Ketamine; Propofol; Computed tomography; Bone biopsy; Morphine

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1. INTRODUCTION

Computed tomography (CT) guided bone biopsy is associated with the highest pain level, ranging from moderate to unbearable pain in approximately 50–70% of cancer patients.[1] Sedation reduces anticipation and anxiety and is usually demanded by patients who have undergone a painful and challenging bone biopsy. Various sedative drugs are currently available for CT-guided bone biopsy. Some clinicians suggest using multiple agents to induce a state of deep sedation.[2]

Propofol is a phenolic derivative used intravenously (IV) as a sedative. It has a rapid onset of effect but a short duration of action, and it does so via activating the receptor of gamma-aminobutyric acid (GABA). Propofol has no analgesic property and has been linked to a drop in blood pressure that increases with dosage because of its direct myocardial depressant effect, decrease in systemic vascular resistance, and respiratory depression. Therefore, adding different additives to propofol may improve its sedative effect and reduce possible side effects.[3]

Dexmedetomidine (DEX) is an alpha-2 receptor agonist which has analgesic, anxiolytic, and sedative effects. DEX may induce bradycardia and hypotension, but it has little respiratory depression.[4] It enhances the effects of other sedatives, such as propofol. Thus, it may be desirable to be added to propofol for deeper sedation. Propofol and Dex have been proposed as an alternative to benzodiazepines for achieving consistent deep sedation with little body movement in preparation for esophageal endoscopic submucosal dissection.[5]

Ketamine acts as an N-methyl-D-aspartate receptor antagonist. It induces dissociative anesthesia and has strong analgesic and amnestic properties. Vomiting, increased salivation, psychotic emergence, and sympathomimetic effects are its main negative implications.[6]

Adding ketamine to propofol (ketofol) has been evaluated for sedation and pain relief for synergistic actions. When used together, ketofol has fewer adverse effects on the cardiovascular and respiratory systems than when used alone. Ketofol can provide efficient analgesia and sedation during bone biopsies. [7]

There is no consensus on the most effective method for sedation and analgesia for bone biopsy. Therefore, we assessed the effectiveness and safety of DEX-propofol vs ketamine-propofol among cancer patients undergoing CT-guided bone biopsy.

2. METHODOLOGY

This randomized, double-blind study was done on 60 adult cancer patients aged 18-60 y, ASA physical status II, who underwent CT-guided bone biopsy. The study was approved by the Ethical Committee and registered on ClinicalTrials.gov (ID: NCT05752903). The study was done from March 2023 to September 2023. All patients provided signed consent. The study complied with the Declaration of Helsinki, 2013, and adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Allergy to any of the utilized medications, or patients suffering from kidney failure or bleeding diathesis, and severe lung, heart, and liver disorders were excluded.

2.1. Randomization and blindness

The patients were randomly assigned into two equal groups using a computer-generated parallel approach and sealed opaque envelopes. Group D received DEX + propofol. Group K: received ketamine + propofol. A non-participant pharmacist prepared the drugs. The participants and care providers were blinded by the drug administered.

A pre-procedure assessment was done by taking a history and conducting a clinical and laboratory examination. The patients were given guidance about using the visual analog scale (VAS).

Upon arrival at the operating room, an IV cannula was inserted. Parameters monitored were temperature, pulse oximetry, 5-lead ECG, non-invasive blood pressure and capnography.

Group D received DEX 1 µg/kg + propofol 2.5 mg/kg IV, then continued with DEX 0.5 µg/kg/h + propofol 2.5 mg/kg/h as infusion. Group K received ketamine 1 mg/kg + propofol 2.5 mg/kg IV, then continued with ketamine 0.25 mg/kg/h + propofol 2.5 mg/kg/h as infusion. Oxygen 2 L/min through nasal canula was used in all patients.

The sedation level was measured using the Ramsay Sedation Scale (RSS), which ranged from 1 to 6.

Rescue sedation was achieved by propofol 0.5 mg/kg IV bolus to achieve RSS 4 to 5. The additional dosage of propofol was noted after the surgery was completed. Recovery time was recorded. Oxygen was provided to all patients in the recovery with oxygen masks. Patients were discharged from the ward when the modified Aldrete score was 9.

Before receiving either DEX or ketamine, the subjects' baseline mean arterial pressure (MAP) and heart rate (HR) were recorded every 10 min during intra-procedure and after the procedure every 15 min for one-hour.

Post-procedure pain was measured via the VAS every 15 min for 60 min. If VAS was > 3, 1 g paracetamol infusion. was administered; if VAS was > 6 or > 3 after receiving paracetamol, morphine 3 mg IV was administered. Post-procedure consumption of paracetamol and morphine in the first hour were recorded.

Adverse effects were recorded. Postoperative nausea and vomiting (PONV) was treated by giving 4 mg ondansetron IV. Hypotension, defined by a decrease in MAP by >20% of the baseline value, was managed by reducing the propofol infusion rate, rapidly infusing fluids and incremental doses of ephedrine 3–6 mg. Bradycardia (HR < 50 beats/min) was managed by atropine 0.01 mg/kg IV. Respiratory depression (respiratory rate < 10 breaths/min) was also recorded.

Box 1: The standard table to highlight power analysis elements and to facilitate their acquisition

Power analysis	
We performed the POWER analysis:	
On the primary outcome:	Amount of propofol
Based on the two-tailed statistical test:	Two-independent t-test
And accepting the cutoff for significance (α):	0.05
And a power (1-β) of:	80%
The variability of the primary outcome was:	The mean (SD) amount of propofol used was 68 ± 16.43 mg in the DEX group and 90 ± 34.64 mg in the ketamine group
Based on data taken from:	Five patients were involved in the pilot trial.
We considered as clinically relevant a difference (or a different effect, please specify) of:	22 ± 25.53
Consequently, the effect size was:	0.81
The sample size needed was:	25 in each group
The sample size increased to allow the dropout rate, and the total sample size needed was:	30 in each group

Consumption of propofol was the primary outcome; the secondary outcomes were hemodynamic parameters, VAS pain scores and the adverse events.

2.2. Sample size calculation

G*Power 3.1.9.2 (University of Kiel, Germany) was used for the sample size calculation. Five patients were involved in the pilot trial, and the mean ± SD amount of propofol used (the primary outcome) was 68 ± 16.43 mg in the DEX group and 90 ± 34.64 mg in the ketamine group. The confidence limit was 95%, the power was 80%, and the group ratio was 1:1, with the addition of five patients for dropouts. Therefore, 30 patients were recruited for each group (Box 1).

2.3. Statistical analysis

The statistical tests were done in IBM's SPSS v27 (Armonk, NY, USA). To determine if the data were normally distributed, we used histograms and the Shapiro-Wilks test. The unpaired Student t-test was used to calculate means and standard deviations for parametric quantitative variables. Median (Interquartile Range) values were calculated using the Mann-Whitney U test for non-parametric quantitative variables. The $\chi 2$ or Fisher's exact test converted qualitative variables into numerical frequency distributions and percentages. The significance level was $P < 0.05$.

3. RESULTS

Out of 84 patients who were initially screened for this trial, 18 were found to be ineligible, and six refused to participate. The rest of the patients were equally randomized (30 patients each). Statistical analysis and follow-up were done for all patients (Figure 1). Demographic data and the procedure duration were similar between groups (Table 1).

Table 1: Demographic data and procedure duration between groups

Parameter		Group D (n = 30)	Group K (n = 30)	P
Age (y)		40.37 ± 11.09	39.37 ± 10.38	0.720
Gender	**Male**	21 (70)	18 (60)	0.417
	Female	9 (30)	12 (40)	
Weight (kg)		73.3 ± 6.13	71.43 ± 5.4	0.216
Height (m)		1.7 ± 0.07	1.71 ± 0.06	0.712
BMI (kg/m^2)		25.46 ± 3.07	24.6 ± 2.63	0.251
ASA physical status I and II		30 (100)	30 (100)	---
Procedure duration (min)		24.33 ± 4.1	24.83 ± 4.04	0.636

Data are presented as mean ± SD or frequency (%). BMI: Body mass index.

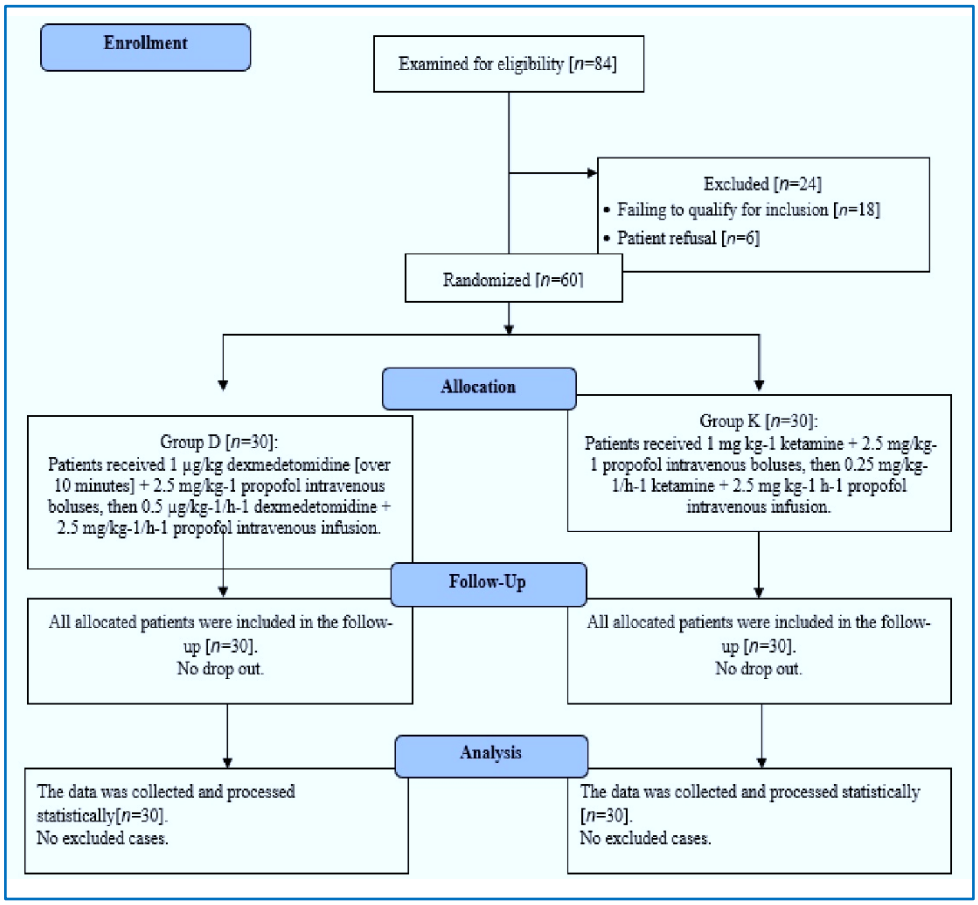

Figure 1: CONSORT flowchart of the enrolled patients

Table 2: Propofol, paracetamol, and morphine consumption in the two groups

Variable	Group D (n = 30)	Group K (n = 30)	P
Total additional intra-procedure propofol consumption (mg)	35 (0 to 70)	70 (40 to 95)	< 0.001*
Patients required paracetamol	19 (63.33)	26 (86.67)	0.037*
Patients required morphine	8 (26.67)	19 (63.33)	0.004*
Post-procedure total morphine consumption (mg)	0 (0 to 2.25)	3 (0 to 3)	0.003*

Data presented as median (IQR) or n (%); P < 0.05 considered as significant

Table 3: Comparative VAS scores in two groups

Time	Group D (n = 30)	Group K (n = 30)	P
15 min	1 (0 − 2)	2 (1 − 2)	0.010*
30 min	2 (1 − 3)	4 (2 − 4)	0.001*
45 min	2.5 (2 − 5)	4 (2 − 6)	0.119
60 min	3.5 (2 − 5)	3.5 (2 − 6)	0.195

Data presented as median (IQR) or n (%); P < 0.05 considered as significant

The median (IQR) of total additional intra-procedure propofol consumption was 35 (0 to 70) mg in Group D and 70 (40 to 95) mg in Group K. Patients who required paracetamol were 19 (63.33%) patients in Group D and 26 (86.67%) patients in Group K. Patients who required Morphine were 8 (26.67%) patients in Group D and 19 (63.33%) patients in Group K. The median (IQR) total morphine consumption within one hour of the procedure was 0(0 to 2.25) mg in Group D and 3(0 to 3) mg in Group K. Total intra-procedure propofol consumption, patients requiring Morphine and paracetamol consumption within one hour post-procedure, and total morphine consumption within one-hour post-procedure were statistically reduced in Group D compared with Group K ($P < 0.05$) (Table 2).

HR and MAP measurements at baseline and 45 min and 60 min post-procedure showed no considerable variation between groups. In comparison, at 10 min, 20 min, end of the procedure and 15 min, 30 min post-procedure were lower considerably in Group D compared with Group K ($P < 0.05$) (Figure 2).

VAS measurements were reduced

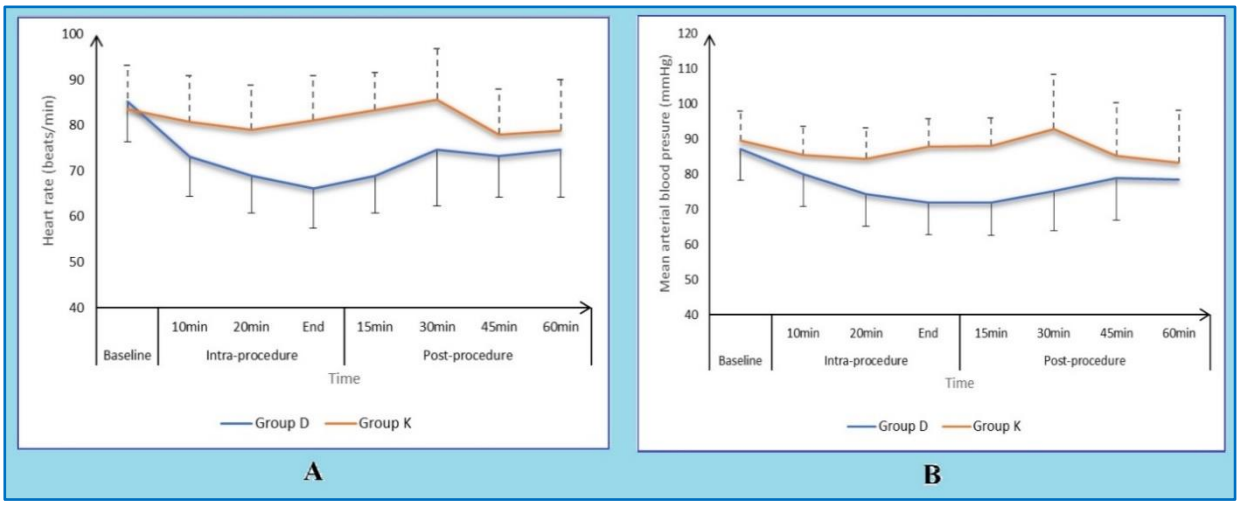

Figure 2: (A) Heart rate (beats/min) and (B) mean arterial pressure (mmHg) changes between groups

significantly at 15 min and 30 min in Group D compared with Group K (P = 0.010 and 0.001, respectively) and were insignificantly different at 45 min and 60 min between groups (Table 3).

Group D had a considerably shorter recovery than Group K (P < 0.001). Adverse incident frequency (PONV, bradycardia, hypotension and apnea/respiratory depression/hypoventilation) was equivalent between groups (Table 4).

4. DISCUSSION

According to our findings, patients who required Morphine and paracetamol within one h post procedure and recovery time were considerably reduced in Group D compared with Group K, so they had better analgesic effects. They can be used in some painful procedures. Total intra-procedure propofol consumption was considerably reduced in the D Group than in the K Group. VAS measurements were lower notably at 15 min and 30 min in Group D than in Group K post-procedure.

Table 4: Recovery time and adverse events of studied groups

Variable	Group D (n = 30)	Group K (n = 30)	P
Recovery time (min)	6.13 ± 2.33	23.27 ± 8.59	< 0.001*
Adverse events			
PONV	3 (10)	8 (26.67)	0.095
Hypotension	7 (23.33)	3 (10)	0.166
Bradycardia	4 (13.33)	2 (6.67)	0.389
Apnea/ respiratory depression/ hypoventilation	5 (16.67)	9 (30)	0.222

Data are presented as mean ± SD or n (%); P < 0.05 considered as significant

Propofol has been proposed as a sedative for use during biopsies, but it has many adverse effects.[8] The benefits of adding a sedative or analgesic to propofol include providing a better sedation profile, decreasing propofol dose, and maintaining respiratory reflexes; however, this can cause further difficulties.[3]

DEX has been demonstrated to minimize stress response to surgery and agitation in the critical care setting through its analgesic and sedative properties generated by the activation of alpha-2 receptors in the pons locus coeruleus of the brainstem.[9, 10]

The negative effects of ketamine, such as hallucinations, increased secretions, and vomiting, are mitigated when propofol is added. Meanwhile, ketamine's analgesic effect maximizes the propofol effect.[4] Ketamine's precise mechanism of action is still unknown. However, blocking signals from the frontal to the brain's parietal lobes is the most likely reason for general anesthesia.[11] Similar to our results, Ghadami Yazdi et al. verified that the lower doses of ketamine compared with propofol give similarly acceptable sedation and analgesia with lower recovery time and maybe a better alternative for patients undergoing bone marrow aspiration.[12] Moreover, Silva et al. showed that Ketofol could produce efficient analgesia and sedation during pediatrics medical procedures undergoing a bone biopsy, with low pain scores and short recovery time.[13]

Elzohry et al. confirmed that the DEX-propofol group required significantly less total propofol during endoscopic retrograde cholangiopancreatography compared with the ketamine-propofol one.[14]

On the contrary to our research, Sruthi et al. concluded that for diagnostic transesophageal echocardiography (TEE), ketofol is preferable to DEX since it takes less time to establish adequate sedation.[15] Contradictory findings were found by El Mourad and coworkers, who found that the ketamine-propofol group required less propofol than the DEX-propofol group.[16]

In the current study, HR and MAP measurements at 10 min, 20 min, end-procedure, and 15 min, 30 min post-procedure in Group D had been much lower than Group K. Adverse events (PONV, hypotension, and bradycardia) were statistically comparable. Since DEX is a highly selective -2 adrenergic agonist with sedative and analgesic characteristics, this may explain why the DEX-propofol Group had a greater rate of hypotension and bradycardia. It enhances sympatholytic activity, minimizes the stress response, and improves sedation by affecting hemodynamic stability.[17]

Ketamine has direct and indirect sympathomimetic effects on the cardiovascular system induced by the inhibition of catecholamine reuptake via multiple mechanisms. Induction with a combination of propofol and ketamine reduces the suppression of hemodynamic and cardiac processes normally observed with propofol alone.[18] Previous controlled trials indicate that hypotension and bradycardia are less common in individuals receiving ketamine for sedation.[15, 19] Yin et al. observed that among elder patients undergoing gastrointestinal endoscopy, fewer incidences of hypoxia, hypotension, and bradycardia were honored with the combination of propofol and ketamine at 0.4 mg/kg^{-1}, indicating that it maintained hemodynamic and respiratory stability.[19] Moreover, Bachula et al. found that the ketamine-propofol group had steady hemodynamic parameters throughout and after the surgery.[20]

Moreover, other researchers reported that combining ketamine and propofol contributed to more stable hemodynamics and fewer side effects in patients undergoing bone marrow aspiration.[12, 13] Moreover, it was showed that no patients required airway intervention in patients of Ketofol use during medical procedures in children undergoing a bone biopsy. Ketofol was proved to be preferable to DEX in terms of fewer hemodynamic disturbances and post-procedure consequences for diagnostic TEE.[15, 21]

On the contrary Tekeli et al. found that DEX-propofol was associated with more stable hemodynamics. The different doses of DEX, ketamine, and propofol could explain the conflicting results.[4]

El Mourad and his colleagues agreed with our findings that the ketamine-propofol combination is more hemodynamically stable than the DEX-propofol combination during awake fibreoptic intubation.[16, 22]

5. LIMITATIONS

This research was conducted at a single location, with a small sample size, and hence, its results cannot be generalized to the wider population. Future studies should include those in the highest risk category (ASA III), and with a wider variety of sedative drugs, concentrations, and volumes.

6. CONCLUSION

Dexmedetomidine-propofol had superior sedation efficacy as noted through lower pain scores, less intraoperative propofol, morphine and paracetamol consumption, and shorter recovery time during CT-guided bone biopsy. On the other hand, ketamine-propofol exhibited superior hemodynamics stability, as shown by more consistent HR and MAP.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved. The authors have no conflicts of interest.

9. Authors' contribution

ASA: Concept, Data curation, Formal analysis and Funding acquisition
NOAZ: Investigation and Methodology.
AMA: Project administration, Visualization. Roles/Writing - original draft; and Writing - review & editing.
ASA: Software and Supervision, Validation.

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