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Original Article

Impact of Ketamine-Propofol Combination (Ketofol) Versus Ketamine Alone on Blood Glucose Levels in Patients Undergoing Total Intravenous Anesthesia: A Hospital-Based Clinical Study

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Abstract

Background: Blood glucose regulation is critical during the perioperative period. Hyperglycaemia or diabetes mellitus presents challenges in managing surgical patients, as high glucose levels can increase morbidity and mortality. This study compared the impact of a ketamine-propofol combination (ketofol) versus ketamine alone on blood glucose levels during the induction phase of total intravenous anaesthesia in patients at a regional hospital in Timor-Leste. Understanding the differential effects of these anaesthetic agents is crucial for optimising perioperative care in patients with diabetes. **Methods**: This experimental study was conducted at a regional hospital in Timor-Leste and included 62 patients undergoing total intravenous anaesthesia. Patients were randomly assigned into two groups: Group A received a ketamine-propofol combination (ketofol), while Group B received ketamine alone. Blood glucose levels were measured at baseline and at 5, 10, 15, and 20-minutes post-induction. Ethical clearance was obtained from the Health Research Ethics Committee of Timor-Leste. Statistical analysis was performed using descriptive statistics, independent t-tests, and Pearson's correlation to assess the differences in glucose levels between the groups. **Results**: A total of 62 patients were included in the study, with 31 patients receiving ketofol and 31 patients receiving ketamine alone. Blood glucose levels were measured at four time points: T1 (5 min post-induction), T2 (10 min post-induction), T3 (15 min post-induction), and T4 (20 min post-induction). No significant differences were observed between the two groups at T1 and T2. However, at T3 and T4, the Ketamine group exhibited significantly higher blood glucose levels than the ketofol group ($p = 0.001$). **Conclusion**: These findings suggest that the combination of ketamine and propofol (ketofol) provides better control of blood glucose levels, particularly during the later stages of anaesthesia.

Keywords: Ketamine, Propofol, Ketofol, Blood Glucose Levels, Total Intravenous Anaesthesia, Hyperglycaemia.

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INTRODUCTION

The regulation of blood glucose is a crucial component of metabolic homeostasis, particularly during the perioperative period. In surgical patients, fluctuations in blood glucose levels, especially among those with hyperglycaemia or diabetes mellitus (DM), pose significant challenges to anaesthesiologists. Inadequate glucose control during the perioperative period can result in increased morbidity and mortality, particularly in patients with diabetes. Diabetes mellitus has emerged as a major global public health concern, with the International Diabetes Federation reporting 382 million individuals living with diabetes in 2013, a figure projected to increase to 592 million by 2035. In Indonesia,

approximately 6.9% of individuals over the age of 15 years are affected by diabetes, highlighting the growing burden of this disease within the population [1,2].

Effective management of blood glucose levels during surgical procedures is essential, particularly for patients with diabetes. Surgical intervention elicits significant stress responses mediated by the neuroendocrine system, leading to the release of catecholamines, glucagon, and cortisol, which can elevate the blood glucose levels. In non-diabetic patients, insulin secretion is generally sufficient to counteract stress-induced hyperglycaemia. However, this homeostatic mechanism is compromised in patients with diabetes, rendering glucose management during anaesthesia critical for optimising surgical outcomes [2,3].

Enhanced Recovery After Surgery (ERAS) protocols emphasise managing glucose levels preoperatively, intraoperatively, and postoperatively to improve patient outcomes. For diabetic individuals, effective glucose regulation is crucial to prevent complications such as delayed gastric emptying, aspiration pneumonia, and neuropathy [4]. Intravenous anaesthesia is key to controlling glucose fluctuations during induction. Agents such as propofol, ketamine, and thiopental are commonly used in total intravenous anaesthesia (TIVA) owing to their sedative, analgesic, and haemodynamic properties [5].

Ketamine increases cerebral blood flow and oxygen consumption and elevates blood glucose levels owing to its sympathomimetic effects and glucocorticoid-like activity [3,6]. Propofol generally reduces blood glucose levels, potentially causing hypoglycaemia in some patients [2]. The ketamine-propofol combination (ketofol) is increasingly used for anaesthesia induction; however, its effect on blood glucose regulation is debated. Some studies suggest that ketofol may also raise blood glucose levels, especially in diabetic patients [7-10].

This study aimed to compare the effects of ketofol versus ketamine alone on blood glucose levels during induction in patients undergoing total intravenous anaesthesia. By examining the impact of these anaesthetic agents on glucose metabolism, this research seeks to provide insights to enhance perioperative care in diabetic surgical patients. These findings may inform anaesthesia management strategies to reduce perioperative complications in this vulnerable population.

MATERIALS AND METHODS

This study was conducted as an experimental investigation to evaluate the effects of blood glucose levels during induction using a ketamine-propofol combination (ketofol) compared to ketamine alone in patients undergoing total intravenous anaesthesia. The research was conducted at a regional hospital in Timor-Leste, specifically within the Surgery and Integrated Diagnostic Units.

The study population comprised patients undergoing total intravenous anaesthesia at the hospital. Inclusion criteria encompassed patients aged 18-65 years, classified as American Society of Anesthesiologists (ASA) I-II, with normoglycaemic status and a body mass index (BMI) ranging from 18.5 to 24.9 kg/m^2. Exclusion criteria included contraindications for propofol or ketamine administration and any severe cardiovascular or respiratory emergencies during the perioperative period. Patients requiring additional rescue interventions or sedation within 20 min post-induction were also excluded from the analysis.

A total of 62 patients were enrolled in the study and randomly assigned to two groups using simple random sampling. Group A received an intravenous combination of ketamine and propofol (Ketofol) in a 1:1 ratio (100 mg ketamine mixed with 100 mg propofol), whereas Group B received intravenous ketamine alone at a dose of 1 mg/kg body weight. Blood glucose levels were measured at baseline and at 5, 10, 15, and 20-minutes post-induction using a standard glucose meter (GlucoDr).

The research procedure commenced with obtaining ethical clearance from the Health Research Ethics Committee of Timor-Leste. Following approval, patients were enrolled

based on the inclusion and exclusion criteria. All participants were informed of the study objectives, procedures, potential risks, and benefits, and written informed consent was obtained prior to their participation.

Once the patient was prepared for surgery, the baseline blood glucose level was measured. Standard monitoring equipment was used. Premedication, including sulfas atropine (0.01-0.02 mg/kg) and midazolam (0.05 mg/kg), was administered intravenously.

For induction, Group A received an intravenous ketofol combination (100 mg ketamine mixed with 100 mg propofol), with each dose of 1 ml per 5 kg body weight. Group B received intravenous ketamine (1 mg/kg body weight). After induction, blood glucose levels were measured at 5, 10, 15, and 20-minutes post-induction to assess changes over time.

Blood glucose levels were recorded for analysis. A standardised emergency protocol was followed, ensuring that the necessary emergency equipment was available. All clinical staff were trained to promptly handle adverse events.

Data were analysed using descriptive statistics to examine the variable frequency distribution. For normally distributed data, an independent t-test was used to compare blood glucose levels between the groups. Pearson's correlation test identified significant relationships, with significance set at $p<0.05$. This study adhered to the ethical guidelines and was approved by the Health Research Ethics Committee of Timor-Leste (Ethical Clearance No. 2019/77-01/MOH/TL). Informed consent was obtained from all patients.

RESULTS

This study was conducted over a period of one month, from May to June 2019, at a regional hospital in Timor-Leste. The primary objective was to compare blood glucose levels during induction using a ketamine-propofol combination (ketofol) versus ketamine alone in patients undergoing total intravenous anaesthesia. A total of 62 patients who met the inclusion and exclusion criteria were included in this study. Thirty-one patients received ketofol, and 31 patients received ketamine alone. The characteristics of the sample are presented in Table 1. Blood glucose levels were measured at four time points: immediately after induction (T1), 5 min post-induction (T2), 15 min post-induction (T3), and 20 min post-induction (T4).

Table 1. Sample Characteristics

Characteristic	Ketofol Group (n=31)	Ketamine Group (n=31)	Total (n=62)	p-value
Gender, n (%)				
Male	21 (50%)	21 (50%)	42 (67.7%)	0.001
Female	10 (50%)	10 (50%)	20 (32.3%)	
Age (mean ± SD)	41.42 ± 1.36	45.58 ± 0.44		0.001
Procedure Type, n (%)				
Gastroscopy	13 (43.3%)	17 (56.6%)	30 (48.4%)	
MRCP	3 (50%)	3 (50%)	6 (9.7%)	0.001
Bronchoscopy	8 (57.1%)	6 (42.9%)	14 (22.6%)	
Colonoscopy	7 (58.3%)	5 (41.7%)	12 (19.4%)	
ASA Classification, n (%)				
ASA 1	7 (53.8%)	6 (46.2%)	13 (21%)	0.001
ASA 2	24 (49%)	25 (51%)	49 (79%)	
Pre-procedure KGDS (mean ± SD)	100.7 ± 2.3	119.4 ± 5.1		0.166
Total	31 (100%)	31 (100%)	62 (100%)	

Note: The p-values indicate the statistical significance of differences between the two groups. A p-value of less than 0.05 denotes a statistically significant difference

As shown in Table 1, the gender distribution was equal between the Ketofol and Ketamine groups, with 50% male and 50% female participants in each group. The mean age

in the ketofol group was 41.42 ± 1.36 years, while in the ketamine group it was 45.58 ± 0.44 years. Most patients (48.4%) underwent gastroscopy, followed by bronchoscopy (22.6%), and colonoscopy (19.4%). ASA 2 classification predominated (79%) in both groups. No significant differences were found between the groups regarding sex, age, procedure type, ASA classification, or pre-procedure KGDS levels ($p > 0.05$).

Table 2. Comparison of Blood Glucose Levels (T1–T4)

Group	T1 (Mean ± SD) (mg/dL)	T2 (Mean ± SD) (mg/dL)	T3 (Mean ± SD) (mg/dL)	T4 (Mean ± SD) (mg/dL)
Ketofol	126.8 ± 22.5	152.8 ± 26.6	166.1 ± 28.1	177.8 ± 28.1
Ketamine	121.5 ± 18.9	169.3 ± 43.1	202.7 ± 49.8	226.5± 49.8

Note: T1, immediately after induction; T2, 5 min post-induction; T3, 15 min post-induction; and T4 20 min post-induction

The results indicated no significant differences in blood glucose levels between the Ketofol and Ketamine groups at T1 (immediately after induction) and T2 (5 min post-induction). However, the Ketofol group showed significantly lower blood glucose levels at T3 (15 min post-induction) and T4 (20 min post-induction). At T3 and T4, the Ketamine group had significantly higher blood glucose levels ($p = 0.001$) (Table 2). These findings suggest that ketamine and propofol combination (ketofol) may offer superior glucose control during total intravenous anaesthesia, particularly in later stages. The observed differences in blood glucose levels highlight the potential benefits of ketofol in managing glucose metabolism, which may be especially relevant for diabetic patients undergoing surgery, where maintaining optimal glucose control is crucial to reducing perioperative complications.

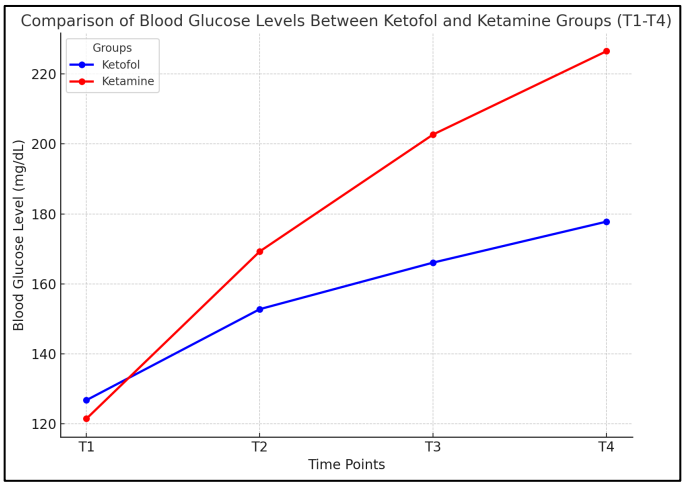

Figure 1. Comparison of Blood Glucose Levels Between Ketofol and Ketamine Groups (T1-T4)

Here is the line graph comparing blood glucose levels between the Ketofol and Ketamine groups at four time points (T1 to T4). The Ketofol group (blue line) showed a steady increase from T1 to T4, with a marked rise after T3. The Ketamine group (red line) also trends upward, with higher values than the ketofol group, especially at T3 and T4. This graph highlights the significant statistical difference at T3 and T4, where the Ketamine group had higher blood glucose levels than the ketofol group (Figure 1).

DISCUSSION

In June 2019, a study at a regional hospital in Timor-Leste compared blood glucose levels during induction with a ketamine-propofol mix (ketofol) against ketamine alone in patients receiving total intravenous anaesthesia. Sixty-two patients participated, with 31 receiving ketofol and 31 receiving ketamine. The results provide insights into how these

anaesthetics affect glucose regulation during the perioperative period. Gastroscopy was the most common procedure, accounting for 48.4% of the sample (Table 1). This aligns with data from a General Hospital in Indonesia (May-July 2015), where gastroscopy was also frequent, underscoring its significance in examining anaesthetic effects on blood glucose. The study noted increased blood glucose levels over time in both groups at intervals (T1 to T4). The mean blood glucose levels at T1 and T2 were higher in the ketamine group than in the ketofol group, although the differences were not statistically significant (Table 2). This aligns with research suggesting that ketamine's sympathomimetic properties may raise blood glucose by releasing catecholamines and stimulating adrenocortical function, increasing glucose production.

At T3 and T4, the difference between the two groups reached statistical significance, with the ketamine group demonstrating higher blood glucose levels than the ketofol group ($p = 0.001$). This observation aligns with the study by Sharma et al., which was conducted on 100 patients in India, in which ketamine administration (2 mg/kg) resulted in elevated blood glucose levels. This increase is attributed to the sympathomimetic action of ketamine, which induces catecholamine release and subsequently activates glucocorticoid function [11-12]. These findings support the hypothesis that ketamine stimulation of the sympathetic nervous system directly influences glucose metabolism, leading to elevated glucose levels during anaesthesia.

Conversely, propofol administration, as observed in the ketofol group, did not result in similar increases in blood glucose levels. Research by Kaviani et al. (2014) indicated that propofol tends to lower blood glucose levels owing to its inhibitory effect on stress response hormones, such as catecholamines and cortisol, which contribute to increased glucose levels [11-14]. This aligns with Johan et al.'s findings that propofol, administered at 2.5 mL/kg body weight, reduced blood glucose levels compared to etomidate induction. This effect is attributed to the capacity of propofol to attenuate the stress response and decrease cortisol and catecholamine secretion [15-20]. Therefore, the combination of ketamine and propofol may offer an advantage in stabilising blood glucose levels during anaesthesia by counterbalancing ketamine's glucose-elevating effects with propofol's glucose-lowering properties.

Figures 1. demonstrated the temporal trend in blood glucose levels for both cohorts, showing that although levels increased in both groups, the elevation was more pronounced in the ketamine group. This suggests that while ketamine alone may induce significant hyperglycaemia, the concomitant administration of propofol (ketofol) appears to mitigate this effect, making it potentially more suitable for maintaining glucose stability, particularly in patients predisposed to hyperglycaemia.

In conclusion, this study underscores the critical influence of anaesthetic agent selection on blood glucose levels during surgical procedures. These findings imply that the combination of ketamine and propofol (ketofol) may offer superior control of blood glucose during anaesthesia, especially in the later stages of surgery. This has significant implications for managing diabetic patients undergoing surgery, where maintaining optimal glucose levels is essential for minimising perioperative complications. Further research is warranted to validate these findings and investigate the long-term effects of ketofol on glucose metabolism.

CONCLUSION

The results indicated that while no significant differences were found in blood glucose levels between the Ketofol and Ketamine groups at T1 (5 min) and T2 (10 min), significant differences emerged at T3 (15 min) and T4 (20 min). Both the intravenous combination of ketamine and propofol (ketofol) and ketamine alone influenced blood glucose levels in patients undergoing total intravenous anaesthesia, with ketofol demonstrating a more favourable effect in stabilising glucose levels during later stages of anaesthesia.

Abbreviations: PONV, T0, Preoperative measurement (baseline); T1, 5 min post-induction; T2, 10 min post-induction; T3, 15 min post-induction; T4, 20 min post-induction; KGDS, Blood Glucose Level; ERAS, Enhanced Recovery After Surgery.

Supplementary Materials: Data sets created and/or examined in this study can be obtained from the corresponding author if requested.

Author Contributions: N.S. was responsible for designing the study, gathering data, and performing the statistical analysis. M.O. provided a critical review, revised the manuscript, interpreted the data, and composed the final version. All authors have reviewed and approved the final manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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