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Effects of Sedation Doses of Propofol and Midazolam on Levels of NGAL, Cystatin-C, KIM-1 in Rats

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ABSTRACT

Limited data are available regarding the impact of their sedation doses midazolam and propofol on early biomarkers of acute kidney injury (AKI). This study aimed to investigate the effects of sedation doses propofol and midazolam on early biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CyC) and kidney injury molecule 1 (KIM-1) of AKI.

A total of 24 Wistar albino rats were separated into three groups (n = 8 per group): a control group (intraperitoneal injection [IP] saline injection once daily for 7 days), a propofol group (IP injection of 2.5 mg/kg propofol once daily for 7 days), and a midazolam group (IP injection of 5 mg/kg midazolam once daily for 7 days). For each group, urinalysis (for urea, creatinine, total protein, NGAL, CyC, and KIM-1) was performed on Day 0 and Day 7; serum analysis (for urea, creatinine, total protein, albumin globulin, ALT, AST, NGAL, CyC, and KIM-1) was performed on day 7.

No significant difference was noted between control, propofol and midazolam groups in terms of Day 7 serum KIM-1, CyC, and NGAL levels and Day 0 and Day 7 urinalysis findings (KIM-1, CyC, NGAL, urea, and creatinine levels).

DISCUSSION AND CONCLUSION: The findings revealed a similar safety profile for seven-day propofol and midazolam administration in rats in terms of the traditional (creatinine, urea) and early biomarkers (NGAL, CyC, KIM-1) of AKI

Keywords: Propofol, midazolam, NGAL, CyC, KIM-1

Introduction

Critically ill patients are frequently treated with continuous-infusion sedative agents for relief of discomfort and anxiety (1-3). Although no ideal sedative drug has yet been identified, midazolam and propofol remain the principal used for sedation in intensive care units (ICUs) (3-5).

Acute kidney injury (AKI) is a major public health problem and is commonly encountered in critically ill patients; it has an incidence that ranges from 36–67% during an ICU stay (6-10).

Early detection of AKI is crucial for preventing or limiting its hazards, such as increased risk of mortality, prolonged hospital stay, and greater financial cost (11,12). Given the failure of traditional biomarkers (creatinine, urea, urine output) to aid in the early detection of AKI, investigators have focused on AKI's early biomarkers (11). Neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CyC), and kidney injury molecule-1 (KIM-1) are amongst the several promising early biomarkers of AKI (11).

NGAL is a marker of tubular injury with an increase in concentration in response to tubular stress >24 hours before rises in serum creatinine (13,14). Plasma NGAL has been shown to predict the duration of AKI, length of stay, and mortality (15-17). CyC is another marker of tubular stress, but in contrast to NGAL, serum levels are determined by glomerular filtration, and changes in levels reflect changes in GFR; it predicts AKI better than serum creatinine, but it is not superior to NGAL (11,14,18,19) KIM-1 is a transmembrane glycoprotein that is upregulated in proximal tubular cells after ischemic or nephrotoxic injury and shown to be associated with the detection of existing AKI (11,20).

Propofol and midazolam are considered to enable equally safe and effective short-term sedation overall, while propofol is also considered to be superior to midazolam in terms of concomitant antioxidant and anti-inflammatory properties and more favorable

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pharmacokinetic profile enabling safer use in patients with liver disease (5,10, 21, 22-25).

Researchers have also suggested propofol's potential renoprotective role via the inhibition of proinflammatory cytokines in ischemia/reperfusion or sepsis, injury in animal models as well as in clinical studies among critically ill patients and cardiac, colorectal, and cardiopulmonary bypass surgery patients (10,26,27,28,29,30).

However, most of the studies have addressed the renal effects of propofol or midazolam during surgery anesthesia rather than their administration for sedation in critically ill patients and focused on AKI's traditional (creatinine, urea) rather than early biomarkers (NGAL, CyC, KIM-1) (10,31-33).

This study was therefore designed to investigate the renal and hepatic effects of propofol and midazolam as sedative agents in rats via an analysis of both AKI's traditional (creatinine, urea) and early biomarkers (NGAL, CyC, KIM-1) alongside the hepatic function indexes.

Methods and Material

Animals and Experimental Groups: A total of 24 Wistar albino rats (≥8 weeks of age and weighing 180–350 g) were kept in a light- and temperature-controlled room with a 12 hr light–dark cycle, a temperature of 22°C, and relative humidity of 30–70%. The animals were fed standard rat pellets and provided with water ad libitum. Our University Animal Research Ethics Committee approved the study (date of approval: 31.01.2019; protocol no: 2019/01). This study was conducted in our University Experimental Medicine Application and Research Center between 04.10.2018 and 12.10.2018

Study Protocol: The rats were separated into three groups (n = 8 per group), including a control group (CON; intraperitoneal saline injection once daily for 7 days), a propofol group (PRO; intraperitoneal injection of 2.5 mg/kg propofol [Diprivan®, 1%, iv flacon, 10 mg/ml] once daily for 7 days), and a midazolam group (MID; intraperitoneal injection of 5 mg/kg propofol [Demizolam®, iv flacon, 5 mg/ml] twice daily for 7 days). Urine samples for a 24 h urinary analysis were collected on Day 0 and Day 7 of the experimental period from each group. The rats were sacrificed via exsanguination under 75 mg/kg ketamine (Ketalar® flacon, Pfizer Inc, Istanbul, Turkey) and under 10 mg/kg xylazine anesthesia (Rompun® flacon, Bayer Inc, Germany) the day after the final urine sample collection. Serum samples for biochemical analysis and kidney and liver tissue samples for histopathological analyses were also collected.

Serum and Urinalyses: Serum analyses for urea, creatinine, total protein, albumin globulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urinalysis for urea and creatinine were performed spectrophotometrically with a Ci16200 model autoanalyzer commercial kits (Abbott®). Serum and urinalyses for NGAL (Catalog number: YLA 0724HU), CyC (Catolog number: YLA 1444HU), and KIM-1 (Catalog number: E-EL-H0186) levels were performed using commercial kits featuring the ELISA method and a Bio-Tek 800 device.

Histopathological Analysis: Liver and kidney tissue samples were fixed in 10% buffered formalin for 48–72 hr and then trimmed and processed for routine histopathological examination. Tissue samples were embedded in paraffin for serial sectioning. Longitudinal 4–5 μm sections were stained with hematoxylin and eosin (HE) and examined under a light microscope (Leica DMRB, Germany); images were also taken via the attached camera (Basler Ace, Germany). The same pathologist, who was unaware of the experimental groups, performed all the histopathological analyses.

Statistical Analysis: Data were analyzed using SPSS 25.0 (Armonk, New York: IBM Corp.) and PAST 3 software (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological Statistics). Normality test was assessed using Shapiro-Wilk test and the homogeneity of variance was evaluated by Levene's test. Multiple independent groups were compared using One-Way ANOVA test followed by post hoc Fisher's Least Significant Difference (LSD) test for continuous variables and using Kruskal-Wallis H Test followed by Monte Carlo simulation for categorical variables. Twice-repeated measurements were compared using Wilcoxon signed-rank test for dependent continuous variables, and the interaction of repeated quantitative measurements of the variables according to the groups was evaluated using Repeated Measure ANOVA (RANOVA) test. Continuous variables were presented in the tables as mean±standard deviation (SD), interquartile range (IQR), and median (minimum/maximum) and categorical variables were expressed as frequencies (n) and percentages (%). Variables were analyzed at 95% confidence level and *p* value less than 0.05 was considered significant.

Results

Serum Analysis Findings on Day 7: On Day 7, the serum AST levels were significantly higher in the propofol group compared to the midazolam group (Table 1) ($p < 0.05$). The serum urea levels were

Table 1. Serum Analysis (Day 7) Findings in Study Groups

	Control serum	Propofol serum	Midazolam serum	P
	Mean±SD	Mean±SD	Mean±SD	
KIM-1	1.00±0.10	0.83±0.27	0.74±0.18	0.054
NGAL	6.98±0.66	6.15±1.79	5.86±1.10	0.182
CYS-c	10.43±2.53	9.09±2.61	6.63±2.92	0.084
AST	90.29±7.36AB	106.14±18.60 A	83.00±12.45B	0.042
ALT	27.00±4.16	27.75±2.66	25.20±4.27	0.569
ÜRE	45.43±4.89A	38.50±3.85AB	33.60±3.51B	0.001
CRE	0.57±0.02	0.58±0.03	0.56±0.04	0.629
ALB	31.00±1.15	29.50±1.31	30.00±1.87	0.149
TP	62.29±1.80	62.25±1.58	53.00±13.36	0.209

A, B; The difference between groups indicated with different letters is statistically significant. ANOVA; Post hoc test: Fisher's Least Significant Difference (LSD), SD: Standard Deviation

significantly lower in the propofol and midazolam groups compared to the control group (mean ± SD = 38.50 ± 3.85 (ng/ml) and 33.60 ± 3.51 (ng/ml) vs. 45.43 ± 4.89 (ng/ml), respectively; $p < 0.001$ and $p < 0.001$, respectively) (Table 1).

There was no significant difference in the serum KIM-1, CyC, and NGAL levels between the study groups (Table 1).

Urinalysis Findings on Day 0 and Day 7: No significant difference was noted between control, propofol and midazolam groups in terms of Day 0 and Day 7 levels for KIM-1, CyC, NGAL, urea, creatinine and total protein levels as well as in terms of change from baseline for each urinalysis parameter (Table 2).

In addition, no significant change was noted from Day 0 to Day 7 in all urinalysis parameters in each group (Table 2).

Histopathological Findings: The control group showed a normal histological structure in the liver (Fig. 1A and 1B). The propofol and midazolam groups showed mild to moderate microvesicular steatosis (Fig. 1C and 1E) featuring damaged lobular structures, absent or enlarged hepatic sinusoids, enlarged hepatocyte cytoplasm and/or nuclei, blurred boundaries of hepatocytes, and lipid droplets in the cytoplasm. Mononuclear periportal inflammation was also noted in these groups (Fig. 1D and 1F).

The control group showed normal histological architecture in the kidney (Fig. 2A and 2B), whereas increased cellularity in glomerulus (Fig. 2C) was observed in the propofol and midazolam groups; tubular dilatations and moderate interstitial nephritis in the cortex and medulla were also found (Figs. 2D–2F).

Discussion

The findings of the current study indicate no adverse impact of seven-day propofol or midazolam treatment on renal and hepatic function when used at sedation doses in rats with similarly favorable renal safety profile of both agents.

In fact, potential renoprotective effect of propofol has also been suggested in the literature when used for surgery anesthesia whereas AKI outcomes, particularly in relation to early biomarkers of injury, regarding the use of propofol or midazolam as sedative agents remains inconclusive (28-30).

Notably, in contrast to findings of the present study, in a retrospective analysis of propofol and midazolam in critically ill patients, authors reported that propofol was superior to midazolam in terms of providing better renoprotection with lower risk of AKI, and decreased need for renal replacement therapy (10).

In a recent meta-analysis of 52 randomized controlled trials on comparison of sedatives in mechanically ventilated ICU patients, dexmedetomidine was reported to be associated with shorter mechanical ventilation duration than lorazepam, midazolam and propofol, while midazolam was associated with significantly increased risk of delirium and propofol with longer hospital stay, as compared with dexmedetomidine (34).

The present findings do not support the superiority of using propofol over midazolam or vice versa in sedative doses while emphasize the likelihood of both to be a promising and clinically available agent in the critically ill patient setting (10).

Indeed, similar efficacy and safety profile of propofol and midazolam was also reported for prolonged sedation of critically ill mechanically ventilated patients, while the economic profile was considered more favorable for propofol than for midazolam due

Table 2. Urinalysis Findings on Days 0 and 7 in Study Groups

	Control urine	Propofol urine	Midazolam urine	P
	(n=8)	(n=8)	(n=8)	(Intergroup)
	Mean±SD	Mean±SD	Mean±SD	
KIM				
Day 0	1.01±0.30	1.16±0.43	0.96±0.24	0.493
Day 7	1.05±0.40	1.02±0.47	0.89±0.33	0.721
Change (7-0)	0.04±0.59	-0.14±0.65	-0.08±0.21	0.792
p (Intergroup)	0.704	0.846	0.362	
CYS-C				
Day 0	13.12±4.70	13.70±4.04	18.34±5.70	0.108
Day 7	13.09±3.23	16.07±5.02	17.04±4.24	0.186
Change (7-0)	-0.42±6.28	2.29±8.21	-1.30±6.16	0.609
p (Intergroup)		0.503	0.582	
	Median (Min./Max.)	Median (Min./Max.)	Median (Min./Max.)	
NGAL				
Day 0	8.58 (7.00 / 9.42)	8.45 (2.74 / 13.76)	8.49 (5.52 / 13.69)	0.881
Day 7	9.04 (6.49 / 15.25)	8.23 (1.38 / 11.92)	9.97 (6.00 / 12.87)	0.233
Change (7-0)	0.51 (-2.69 / 6.71)	-0.14 (-9.02 / 9.19)	2.11 (-7.69 / 4.47)	0.465
p (Intergroup)		0.642	0.578	
ÜRE				
Day 0	2175 (1056 / 2535)	1595 (977 / 3196)	1493 (1118 / 2225)	0.410
Day 7	1929 (937 / 3069)	1621 (1281 / 3291)	1606 (681 / 2647)	0.611
Change (7-0)	60.50 (-535 / 951)	26 (-1237 / 304)	-179.50 (-742 / 1152)	0.911
p (Intergroup)		0.999	0.999	
CRE				
Day 0	33.11 (19.19 / 51.15)	55.20 (21.43 / 183.13)	35.91 (25.62 / 111.16)	0.464
Day 7	44.93 (18.16 / 94.53)	40.45 (27.70 / 284.77)	28.61 (15.25 / 51.92)	0.216
Change (7-0)	8.77 (-4.99 / 49.72)	-3.54 (-118.01 / 175.65)	-11.04 (-69.82 / 12.61)	0.060
p (Intergroup)		0.642	0.110	
TP				
Day 0	54.75 (17.20 / 72.60)	61.85 (19.80 / 151.20)	41.35 (15.80 / 113.90)	0.843
Day 7	56.15 (12 / 118)	32.30 (26.70 / 83.60)	31.60 (16.60 / 58.40)	0.235
Change (7-0)	-1.35 (-7.70 / 63.60)	0.30 (-105.90 / 9.10)	-7.65 (-94.40 / 31.60)	0.428
p (Intergroup)		0.578	0.384	

RANOVA, Paired T Test, Kruskal Wallis Test, Wilcoxon Signed-Rank Test

to a shorter weaning time associated with propofol administration (35).

Although limited data are available regarding renal adverse impacts of sedative doses of propofol or midazolam, particularly in terms of early biomarkers of AKI, cardiopulmonary risk profile as well as outcomes have been investigated for use of these sedatives in endoscopic procedures (36, 37).

In a meta-analysis of 27 studies in 2518 patients on cardiopulmonary safety of using propofol as compared with traditional agents including midazolam in gastrointestinal endoscopic procedures, propofol sedation was concluded to have a similar risk of

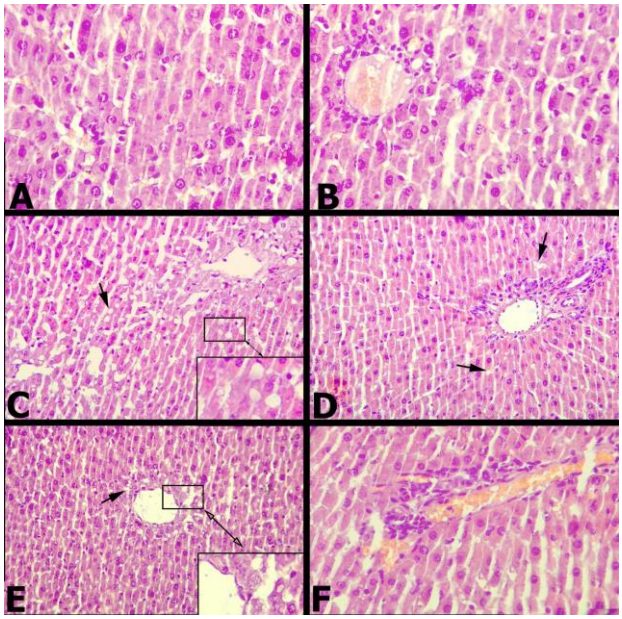

Fig. 1. Histological structure of liver tissue stained with hematoxylin and eosin; magnification 200 X for A and B, 100 X for C–F. A) Normal histological structure of the liver in the control group. B) Normal histological structure of liver in the control group. C) Midazolam-administered rat liver; microvesicular steatosis (arrow); bottom right figure demonstrates high-power magnification of the selected region (black outlined rectangle). D) Midazolam-administered rat liver; microvesicular steatosis (arrows); periportal inflammatory cell infiltration. E) Propofol-administered rat liver; microvesicular steatosis (arrow); bottom right figure demonstrates high-power magnification of the selected region (black outlined rectangle). F) Propofol-administered rat liver; periportal inflammatory cell infiltration

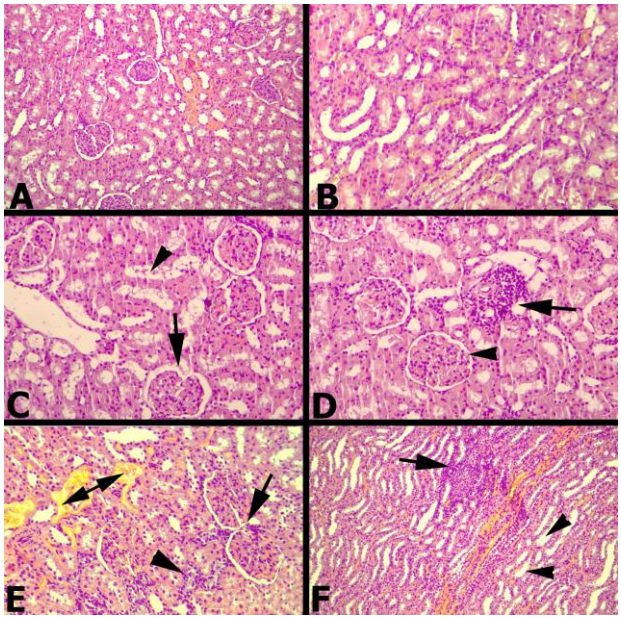

Fig 2. Figure 2A-B. Normal histological architecture of kidney in control group animals. Heamatoxylin and eosin. Magnification 100X. Figure 2C. M administered rat kidney. Increased cellularity in glomerulus (arrow). Loss of lining epithelium and rare sloughing of necrotic cells into lumina (arrow head). Heamatoxylin and eosin. Magnification 100X. Figure 2D. M administered rat kidney. Inflammatory cell infiltration (arrow). Also, glomerulus cellularity is increased. Heamatoxylin and eosin. Magnification 100X. Figure 2E. Propofol administered rat kidney. Increased cellularity in glomerulus (arrow). Inflammatory cell infiltration (arrow head). Casts and tubular dilatations (double headed arrow). Heamatoxylin and eosin. Magnification 100X. Figure 2F. Propofol administered rat kidney. Medullar interstitiel nephritis (arrow). Tubular degenerations (arrow heads). Heamatoxylin and eosin. Magnification 100X

cardiopulmonary adverse events with other agents including midazolam (36).

In an analysis of safety of propofol with and without midazolam for diagnostic upper gastrointestinal endoscopies in children, midazolam-propofol and propofol alone groups were reported to be similar in terms of induction times, sedation times, recovery times and proportion of satisfactory endoscopist responses (40). Authors concluded the efficacy and safety of the sedation protocol using propofol with no additional benefit of midazolam in propofol-based sedation (37).

Although in the current study, propofol administration was associated with higher AST levels as compared with the midazolam group, the histopathological changes were mild and were similar to midazolam group. A transient increase in liver enzymes usually occurs with drugs used for anesthesia induction, but this is not associated with adverse effects unless there is already baseline hepatic impairment (38). Moreover, owing to a favorable pharmacokinetic profile with no need for dose adjustment, propofol is the drug of choice for patients with liver diseases (22-24,26).

It should also be noted that in the present study, sedative agents were used once daily for seven days, which is consistent with their administration for sedation in critically ill patients rather than in anesthesia induction during surgery (10). Accordingly, given the lack of any adverse impact of each agent on renal or hepatic function when used at the recommended dosage for sedation/anesthesia, the present findings emphasize both propofol and midazolam to be sedatives with favorable safety and potential for use in clinical practice. Nonetheless, it is commonly observed that therapeutic and preventive strategies related to AKI that are successful in animal models can fail in human trials (10).

In conclusion, the findings revealed similar safety of 7-day propofol and midazolam administration in rats

in terms of hepatic function indexes and traditional (creatinine, urea) and early biomarkers (NGAL, CyC, KIM-1) of AKI. This seems to be clinically relevant given that these drugs are the two most commonly used sedatives in the critically ill population who are already at high risk for AKI. Accordingly, to be justified in large scale clinical trials in critically ill patient settings as well as different clinical settings with high risk of AKI, the present findings provide experimental evidence on lack of renal hazards even for early biomarkers for AKI in propofol and midazolam treated rats.

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