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RESEARCH ARTICLE

Comparison of Dexmedetomedine-Ketamine Anesthetic Combination to Propofol-Isoflurane in Renal Ischemia-Reperfusion Injury

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ABSTRACT

Perioperative acute kidney injury (AKI) frequently complicates renal ischemia. Anesthesia of such cases may be hazardous. The current study aimed to evaluate and compare the renal protection and anesthetic values of the injected ketamine-dexmedetomidine combination to the inhaled isoflurane pre-medicated with propofol. 20 mongrel dogs were randomized into Propofol-Isoflurane (Pro-Iso) Group: that premedicated with propofol and maintained with isoflurane and Ketamine-Dexmedetomidine (Ket-Dex) Group: that received a combination of ketamine and dexmedetomidine. Heart rate, Respiratory rate, Oxygen saturation and noninvasive mean arterial blood pressure were monitored. Serum levels of Creatinine, Blood Urea Nitrogen and Kidney Injury Molecule-1 (KIM-1) were measured. Tissue Malondialdehyde (MDA) was assessed whereas histopathological assessment was done using a numerical scoring system. The level of KIM-1 decreased 24 hours after the end of reperfusion in dogs anesthetized with Pro-Iso group but remained significantly high for Ket-Dex group. Renal MDA levels for Ket-Dex was significantly higher when compared with Pro-Iso. The numerical scoring system showed significantly lower renal damage for Pro-Iso group. When compared to ketamine-dexmedetomidine, combination of propofol and isoflurane provided more renal protection and effective anesthesia for dogs at risk of perioperative acute kidney injury caused by ischemia-reperfusion injury.

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INTRODUCTION

Perioperative acute kidney injury (AKI) frequently complicates renal ischemia and reperfusion injury (IRI) causing renal damage with no effective therapy. High mortality from this perioperative AKI does not decrease in the previous 50 years (Jones and Lee, 2008).

During IRI, accumulated reactive oxygen species (ROS) results in apoptotic cell death and microvascular damage. ROS, also, results in lipid peroxidation that damages cell membranes and yield toxic metabolites as malondialdehyde (MDA). MDA can be used as a sensitive marker of IRI (Carden and Granger, 2000).

Kidney injury molecule 1 (KIM-1) is a type 1 trans-membrane glycoprotein, that is not detected in healthy but markedly increased following ischemic or toxic renal injury both in serum and urine in animals and humans (Han *et al.*, 2002). Higher KIM-1 levels were correlated to adverse renal outcomes associated with end-stage renal disease (ESRD) and death (Liangos *et al.*, 2007). In mice IRI, the KIM-1 level appeared early and is proportional with the duration of ischemia (Sabbisetti *et al.*, 2014).

Anesthesia of the patients at risk of developing perioperative AKI due to IRI is still a problem. The use of renal protection anesthetics should be of priority in such conditions. Isoflurane is a volatile anesthetic that is widely used in general anesthesia. Volatile anesthetics demonstrated anti-inflammatory effects and produced significant protection of cultured renal proximal tubules through direct activation of cytoprotective kinases (Lee *at*

al., 2006). Su *et al.* (2014) demonstrated that the administration of volatile isoflurane provides preconditioning renal protection effect, which was superior to the treatment with antioxidants. Propofol is commonly used as a premedication for induction of anesthesia before isoflurane use. Yang *et al.* (2013) concluded that propofol protects the kidney against oxidative stress and helps its recovery following IRI.

Ketamine is a commonly used injectable anesthetic with anti-inflammatory properties,that has shown protective effects on IRI in various organs (Sloan *et al.*, 2011). Ketamine-dexmedetomidine combination is widely used as an effective and safe intravenous anesthesia.

Administration of dexmedetomidine (a selective α_2 - adrenergic agonist) before induction of ischemia was found to protect the liver and other organs against the oxidative stress and histological changes of IRI (Chrysostomou and Schmitt, 2008). Results of Yagmurdur *et al*. (2008) suggest that this occurs through inhibition of lipid peroxidation.

The organ protective values of inhalational anesthesia versus the injectable anesthesia withdraw the attention of authors. Řiha *et al*. (2012) compared the cardioprotective effects of ketamine-dexmedetomidine to sevoflurane-sufentanil anesthesia after cardiac surgery.

To the best of our knowledge, the renal protection value of ketamine-dexmedetomidine anesthetic combination were not studied before. This study aimed to evaluate and compare the renal protection value of the injected ketamine-dexmedetomidine combination versus the inhaled isoflurane pre-medicated with propofol. Anesthetic efficacy of both combinations will be also considered.

MATERIALS AND METHODS

Animals: Adult 20 mongrel (14 to 28 kg) dogs were enrolled in a randomized, prospective, blinded study. The dogs were considered to be healthy based on physical examination, hematological and serum biochemical analyses. Animals were fasted the night prior to surgery (approximately 12 hours), but had free access to water. The study was conducted in the animal research facility unit of Mansoura Urology and Nephrology center. The study protocol was approved by the Medical Research Ethics Committee of the Faculty of Mansoura University, Egypt (Code number R/15.11.47. 22/11/2015).

Study design and experimental groups: Animals were randomized into two different treatment groups. The randomization was carried out by a computer random generator number method according to the anesthetic regimen. Propofol-Isoflurane Group (Pro-Iso group) (n=10): animals received propofol as preanesthetic medication 0.5 mg/kg every 10 s until endotracheal intubation could be performed (Monteiro et al., 2014). Anesthesia was maintained with isoflurane (Belda et al., 2012). Ketamine-Dexmedetomidine Group (Ket-Dex group) (n=10): As a preanesthetic medication, animals received a bolus of a combination of ketamine HCL at a dose of 1 mg/kg/IV (ketamine® 50 mg/kg, vial Sigma-Tec Pharmaceutical Industries, Egypt SAE) and dexmedetomidine (Precedex® 100 mcg / ml, preservative free, vial, Hospira, Inc., Lake Forest, IL 60045 USA) at a dose of 1µg/kg/IV. Followed by an infusion of ketamine 25 µg/kg/min + dexmedetomidine 0.5 µg/kg/min. A Sham group (n=5): in which left unilateral nephrectomy was done and right renal pedicle was exposed but without IRI. This group is designed as a control for oxidative stress and renal histopathology.

Methods: Animals in all groups underwent left unilateral nephrectomy through midline incision then ischemia was induced by clamping of the right renal pedicle using atraumatic clamp for 45 minutes then the clamp was released for 60 minutes. The colour of kidney was taken as an index for both renal ischemia and reperfusion.

Preoperative, intraoperative and postoperative physiologic variables monitoring: Heart rate (HR), Respiratory rate (RR), Oxygen saturation and noninvasive mean arterial blood pressure (NIMAP) were monitored by a patient monitor (BMI, Borg Elarab industries, Model MIII, Egypt). They were recorded 15 minutes before anesthetic induction (basal), 10 minutes after induction of anesthesia (Post pre-anesthetics), at the start of surgery, At the onset and 15, 30 and 45 minutes after induction of ischemia, at the end of ischemia (1 hour of reperfusion), at the end of surgery, for 4 hours after termination of surgery at intervals of one hour and 24 hours after surgery.

Measurement of serum levels of chemical biomarkers: Venous blood samples for measurement of biochemical markers were collected preoperatively (basal) and 4 & 24 hours after reperfusion. The clotted blood samples were centrifuged and the serum was stored at -20°C for biochemical analysis.

Serum levels of Creatinine (Cr), Blood Urea Nitrogen (BUN) was measured using an auto-analyzer apparatus (CX7; Beckman, USA). Kidney Injury Molecule-1 (KIM-1) was determined by immunoperoxidase assay using commercial kits (Dog kidney injury molecule-1 detection kits, MyBioSource®).

Collection of tissue samples: Second day of the experiment, dogs were sacrificed with potassium chloride associated with general anesthesia. The right kidney was bisected longitudinally and cut into two equal sized slices. Tissue samples from one half kidney were homogenized for measurement of Malondialdehyde (MDA) as a marker of oxidative stress. The other half of the kidney was fixed in a 4% neutral paraformaldehyde solution for assessment of necrotic injury of proximal tubules. This histo-pathological assessment followed a numerical scoring system as previously detailed (Laverman *et al.*, 2002). The score is graded from 0 to 4 where 0 means normal histology and 4 means severe necrosis.

Statistical analysis: Physiological variables, serum level of biochemical markers and histopathological findings were recorded in all dogs over time; reported as mean ± standard deviation and evaluated by means of repeated-measures ANOVA. Statistical analysis was performed using a statistical software package (SPSS; SPSS Inc. Released 2009. PASW Statistics for Windows,

Version 18.0. Chicago: SPSS Inc.). Significance was defined at P<0.05.

RESULTS

Physiologic variables (Table 1): Compared to basal value, HR in Pro-Iso group showed a significant increase (P=0.01) at the pre-post-anesthetic point. Then, HR showed gradual statistically-insignificant decrease till forty-five minutes' post ischemia when it started to increase again. This increase became significant (P=0.008) 1-hour post-operative. HR retuned around its normal value 3-hours post-operative till the end of observation.

On the other hand, in Ket-dex group, HR showed a general pattern of bradycardia throughout the whole observation. HR returned to normal only 24 hours' post-operative. This decreased HR was significant when compared with basal levels 15, 30 and 45 minutes' post-ischemia, at the end of ischemia, at the end of surgery, 2 hours post-operative (P=0.006, 0.01, 0.02, 0.03, 0.02, 0.04 respectively).

Comparison of both groups showed that HR values in Ket-dex group was lower throughout the whole-time points. This bradycardia was only significant at post pre-anesthetic, end of ischemia, end of surgery, 1 and 2 hours postoperative (P=0.001, 0.04, 0.02, 0.004, 0.05 respectively).

Both anesthetic combinations decreased RR. This decrease was significant at pre-post-anesthetic when compared with the basal value (P=0.02 and 0.002 respectively). RR was significantly decreased more for Ket-dex group when compared with Pro-Iso group (P=0.04). RR is kept constant throughout the whole surgical period in both groups. In Pro-Iso group, RR returned around normal 1 hour postoperative and then showed gradual increase that became significant 3 hours postoperative (P=0.05 when compared with basal value).

On the other hand, RR in Ket-dex group remained decreased after the end of surgery and returned to near normal late. This decrease was significant when compared with basal 1 and 2 hours postoperative (P=0.02). Finally, the bradyapnea that associated Ket-dex combination was significant when compared with the other combination at all 4 hours' postoperative time points (P=0.003, 0.006, 0.003, 0.03 respectively).

Recorded oxygen saturation values were within normal throughout the whole experiment. However, comparison of the two groups showed significant lower levels of oxygen saturation in Ket-Dex group at the onset of surgery, 15 minutes after the onset of anesthesia, at the end of ischemia and at the end of surgery (P=0.05, 0.05, 0.04, 0.002 respectively).

Compared with basal level, MAP in Pro-Iso showed significant sharp drop at the onset of surgery (P=0.001). Thereafter, MAP level increased gradually to a significant rise one hour postoperative (P=0.02) and then returned to the normal level by the end of observation. In Ket-dex group, MAP showed significant increase at the onset of surgery (P=0.003). MAP continued to show this increased pattern that was significant 15 min. after the onset of ischemia (P=0.03), at the end of surgery (P=0.05) and 1 hour postoperative (P=0.007). Thereafter, MAP returns toward normal by the end of observation. Comparing both groups showed higher levels of MAP in Ket-dex than Pro-Iso group that were statistically significant at the time of surgery (P=0.000), 15 minutes (P=0.04) and 30 minutes (P=0.05) after the onset of ischemia, and at the end of ischemia (P=0.04).

Chemical biomarkers (Table 2): Compared with basal levels, Creatinine and BUN showed significant increase 4 (P=0.000 for creatinine & 0.02 and 0.01 respectively for BUN) and 24 hours (P=0.009 for creatinine & 0.006 and 0.000 for BUN) after the end of surgery. Although the serum creatinine and BUN levels were higher for Ket-dex than Pro-Iso group, no statistical significance existed.

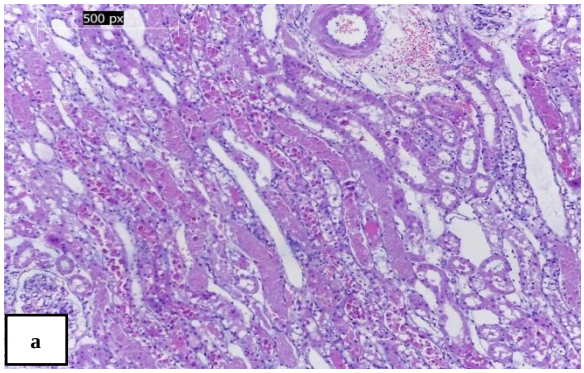
KIM-1 showed increased level 4 hours after the end of reperfusion for both groups. This increase was insignificant when compared with the basal level. The level of KIM-1 decreased 24 hours after the end of reperfusion in dogs anesthetized with Pro-Iso but remains significantly high for Ket-Dex group (P=0.01 when compared with basal & 0.02 when compared with the other group).

Tissue markers (Table 3 & Fig. 1): The MDA level was increased in both groups. This increase was significant when compared with the sham group (P=0.001 for both). MDA level was significantly lower in Pro-Iso group than Ket-Dex group (P=0.009).

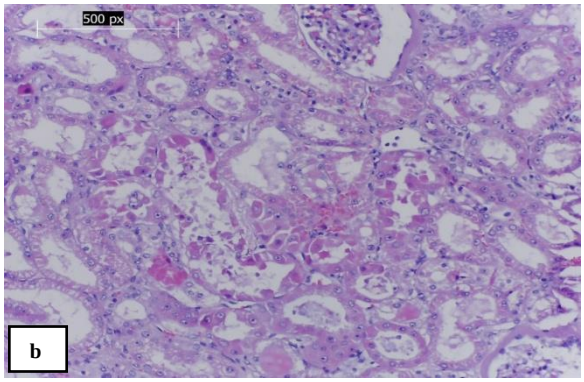
The numerical scoring system score calculated for the renal tissue of the dogs anesthetized with Pro-Iso group was significantly lower than that calculated for Ket-dex group (P=0.03).

Table 1: Comparison of measured vital signs measured between the propofol-isoflurane (Pro-Iso) group and ketamine-dexmedetomidine (Ket-Dex) group at assigned time points. a=significant when compared with basal values, b=significant when compared with pre-post anesthetic, #=Significant when compared with the other group, Significant is ≤0.05

		Heart Rate (beat/ minute)		Respiratory rate / minute		Oxygen Saturation (%)		MAP (mmHg)	
		Pro-Iso	Ket-Dex	Pro-Iso	Ket-Dex	Pro-Iso	Ket-Dex	Pro-Iso	Ket-Dex
Basal		108.8±21.2	110.8±20.3	24.8±5.6	21.5±6.0[a]			110.0±17.9	105.2±9.0
post-induction		144.0±28.1[a]	91.6±32.6 [#]	18.6±8.6[a]	11.5±5.5[#]	97.1±2.0	90.7±9.6	118.9±9.2[a]	121.8±34.9[a]
At surgery		116.4±44.8	82.1±34.1	21.0±0.0	21.0±0.0	98.2±0.8	94.4±5.7[#]	74.6±17.3	127.8±19.2[#]
At onset of ischemia		98.8±27.7	85.2±42.2[a]	21.0±0.0	21.0±0.0	97.8±1.1	94.5±5.7	106.7±27.1	130.4±37.2
After the	15 min.	97.5±20.4	74.0±34.6[a]	21.0±0.0	21.0±0.0	98.2±1.2	95.0±4.6[#]	97.1±33.9	129.9±30.4[a#]
onset of	30 min.	98.8±22.6	75.5±3 5.7[a]	21.0±0.0	21.0±0.0	98.3±1.4	94.3±8.4	93.3±36.3	125.1±31.0[#]
ischemia	45 min.	100.2±21.3	75.9±41.3[a]	21.0±0.0	21.0±0.0	98.6±0.8[b]	94.8±6.3	99.8±34.7	125.1±30.7
End of ischemia		113.9±36.2	74.5±42.0[a #]	21.0±0.0	21.0±0.0	98.6±2.0	91.4±10.0[#]	96.6±27.4	127.7±36.2[#]
End of surgery		110.9±22.9	75.9±37.4 [#]	21.0±0.0	21.0±0.0	98.4±0.8	96.1±1.9[#]	104.6±26.6	125.0±27.3[a]
	1st hour	136.9±33.1[a]	82.8±39.4[a #]	29.2±11.7	15.2±6.0[a #]			125.3±17.6[a]	138.6±29.6[a]
	2nd hour	111.5±29.9	78.7±37.8 [#]	29.4±12.2	16.1±6.0[a #]			104.8±26.2	112.1±33.2
Postoperative	3rd hour	107.2±22.1	87.7±41.9	32.8±11.4[a]	18.2±7.4[#]			122.0±16.1	120.1±25.3
	4th hour	105.9±22.3	94.0±31.6	32.9±14.9	20.4±6.4[#]			121.7±24.0	103.8±25.4
	1st day	107.6±25.9	113.6±25.7	30.1±14.4	22.0±7.7			102.4±17.4	102.4±11.9



a) Normal renal morphology



b) IRI vascular congestion and widespread necrosis

Fig. 1: H & E-stained histological sections (500X) of dog right kidney. A) Sham (normal renal morphology) b) Renal injury (caused by ischemia reperfusion injury - IRI).

Table 2: Comparison of measured chemical biomarkers measured between the propofol-isoflurane (Pro-Iso) group and ketamine-dexmedetomidine (Ket-Dex) group at assigned time points. BUN=Blood urea nitrogen, KIM-1=Kidney injury molecule – 1, a=significant when compared with basal levels, #=significant when compared with the other group, Significant is ≤0.05

		Basal	Post 4 hours	Post 24 hours
Creatinine (mg/dl)	Pro-Iso	1.2±0.2	1.9±0.3[a]	2.3±1.0[a]
	Ket-Dex	1.2±0.2	2.0±0.3[a]	3.0±1.7[a]
BUN (mg/dl)	Pro-Iso	47.0±21.0	63.1±18.6[a]	73.8±25.6[a]
	Ket-Dex	43.8±10.7	56.7±16.1[a]	99.7±37.9[a]
KIM-1 (ng/ml)	Pro-Iso	3.2±1.8	4.6±2.1	3.8±1.2
	Ket-Dex	3.6±1.4	4.8±1.4	5.8±2.1[a #]

Table 3: Comparison of Post 24 hours MDA (nmol/ml) and histopathological score investigated between the propofol-isoflurane (Pro-Iso) group and ketamine-dexmedetomidine (Ket-Dex) group at assigned time points. MDA=malondialdehyde. a=significant when compared with sham. #=significant when compared with the other group. Significant is ≤0.05

	Sham	Pro-Iso	Ket-Dex
Post 24 hours MDA (nmol/ml)	5.2±2.1	10.7±1.2[a]	12.1±0.9[a #]
Histopathological score	0.0	1.3±0.6	2.4±1.4[#]

DISCUSSION

The present study was conducted to evaluate the use of the two common anesthetic combinations in urological procedures in which renal derangement is expected. Ischemia-reperfusion was used as an example of this renal derangement that eventually resulted in perioperative AKI. Their anesthetic efficacy was evaluated in terms of the renoprotective actions and maintenance of well-balanced animal general status was evaluated.

The results of the present study showed that propofol-isoflurane combination conferred more renal protection than the dexmedetomidine-ketamine combination as indicated by significantly lower postoperative levels of KIM-1 and MDA and also better numerical scoring system results. Creatinine and BUN showed also lower levels but with no statistical insignificance.

These results were supported by data reported in the previous studies for either anesthetic agents (single and not in combination). Vasileioua *et al.* (2009) reported that the structural similarity of propofol with vitamin E enables it to suppress lipid perioxidation and explains the cytoprotective effects of propofol. Propofol inhibits nuclear factor- kappa B (NFkB) and thus decreasing production of proinflammtory and oxidative mediators.

Isoflurane also was reported to protect the kidney against ischemia reperfusion injury not only through its antioxidant effect but also through different mechanisms. It modulates endothelium interaction with platelets and neutrophils (Kato and Foex, 2002), increases the formation of phingosine-1-phosphate (S1P) synthesis (Kim *et al.*, 2010), and releases renal tubular TGF-β1 that stimulates adenosine (a known renal vasodilator) formation (Kim *et al.*, 2013). In a study of Carraretto *et al.* (2013), they concluded that the renoprotective value of propofol is equal to that isoflurane, when used against IRI.

Both isoflurane (Zhanga *et al.*, 2011) and propofol (Wang *et al.*, 2007) attenuated the histopathological changes caused by IRI. Thus, combination of both agents is expected to provide more protection. Results of creatinine and BUN can be explained as they are not sensitive biomarker for acute renal changes (Nguyen and Devarajan, 2008).

On the other hand, many literatures demonstrated the renoprotective value of dexmedetomidine for both renal functions and structure. This can be attributed to its anti-inflammatory and antioxidant actions (Carraretto *et al.*, 2013). However, Curtis *et al.* (2011) demonstrated that ketamine in IRI worsened histological renal damage and addition of dexmedetomidine did not save the kidney much.

In study conducted on rats, Yuzera *et al.* (2009) reported that propofol (and not ketamine) significantly protects against IRI as indicated by better histopathological score and lower MDA levels compared with control.

Regarding the vital animal parameters, the present study showed that Pro-Iso combination was better in maintaining the general condition of the patient during the procedure. The use of Dex-Ket combination was associated with bradycardia, bradyapnea, lower oxygen saturation values whereas only MAP showed higher levels. These effects are due to the dexmedetomidine element of the combination and these findings were supported by many literatures (Mahmoud and Mason, 2015).

However, in a recent study, Cheng *et al.* (2014) demonstrated that an intraoperative infusion of dexmedetomidine combined with ketamine caused better sedation, sleep and O_2 saturation and accelerated recovery when compared to sevoflurane-sufentanil anesthetic combination.

The conduction of this study was limited by difficulty to assign a control group for anesthetic experimentation. Instead, we assigned a sham group as a control for oxidative stress and renal histopathology. This work could

be enriched by study of intracellular signal transduction pathways to justify for the differences in potencies.

Conclusions and clinical relevance: When compared to ketamine-dexmedetomidine, Combination of propofol and isoflurane provided effective anesthesia for dogs at risk of perioperative acute kidney injury caused by ischemia-reperfusion injury in terms of renal protection and maintenance of general status.

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Authors contribution: EMN helped in study design, conduction of the practical part, collection of data and manuscript preparation, KIK helped in study design, analysis, and interpretation of data and composition of manuscript. HHS helped in conduction of laboratory investigations and collection of data. HGA helped partly in conduction of the practical part especially in the postoperative animal care. MAH helped in conduction of histopathological investigations and collection of data. WIM helped in conduction of laboratory investigations and collection of data. AARS helped in interpretation of data and manuscript preparation. MMO helped in study design, supervision of the experimental part and manuscript preparation.

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