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Comparison of etomidate and propofol for sedation in outpatient urologic surgeries, a randomized clinical trial

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Abstract : Introduction: Propofol and etomidate are popular hypnotic agents in outpatient settings. We studied sedative, hemodynamic, and adverse effects of these two drugs in patients undergoing outpatient urologic surgeries.

Methods: In this randomized clinical trial, 177 patients aged 50 years and older were recruited, and devided into an etomidate and propofol group, according to whether they were sedated by repeated bolus doses of etomidate and propofol. Recorded data included demographic characteristics, heart rate (HR), respiratory rate (RR), blood pressure (BP), oxygen saturation (Spo_2), patients', anesthesiologists' and urologists' satisfaction, sedation and pain scores, hemodynamic and respiratory side effects.

Results : Sedation scores were comparable between groups but, compared to etomidate, propofol induced a greater decrease in systolic, diastolic and mean arterial blood pressures (P-values < 0.01). HR showed no significant difference between groups. Propofol showed a lower RR only at the time before transfer to the ward (P-value 0.0001). Anesthesiologist satisfaction was significantly higher with etomidate than propofol (P-value 0.04).

Conclusions : Our study demonstrates that both etomidate and propofol can induce satisfactory sedation in patients undergoing outpatient urologic surgeries. Major hemodynamic and respiratory complications were more frequent with propofol than etomidate. However, myoclonus and pain at the injection were higher in the etomidate group.

Keywords : propofol ; etomidate ; outpatient urologic surgery ; sedation.

Introduction

Urologic procedures are commonly performed on an outpatient basis. This can be associated with surgical and anesthetic complications such as post-surgical pain, local bleeding, hematuria, urinary retension, fever and re-admission (1). Factors that have been associated with complications after urologic procedures include older age, American Society of Anesthesiologists (ASA) classification, pre-operative transfusion and preoperative renal dysfunction (2). Moreover, postoperative complications of ambulatory urologic procedures are associated with the type of the anesthetic agent. As a consequence, the used anesthetic agent should allow fast recovery, be associated to a low incidence of adverse effects; provide sufficient sedation, low pain severity, and early discharge time (3).

Propofol and etomidate are among the most common anesthetic drugs. They are used for sedation in many procedures, but have their own advantages and disadvantages. The comparison of the adverse effects between etomidate and propofol have been performed for various procedures, such as gastroscopies, endoscopic retrograde cholangiopancreatography (ERCP), and cardioversion. Those comparisons have established etomidate as a more suitable drug for sedation and analgesia, with more stable hemodynamic responses, and less adverse events (4-6).

To the best of our knowledge, there is only one study comparing the effect of propofol and etomidate for short-time urologic procedures (7). However, this study had a small sample size, and was flawed by some methodological issues.

Due to the high prevalence of ambulatory urologic surgical procedures, and the paucity of evidence regarding supremacy of one of the two agents for these procedures, the present study aimed at comparing hemodynamic instability and intra and postoperative side effects between propofol and

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etomidate driven sedation in a randomized clinical trial.

Methods

This study was a double-blind randomized clinical trial approved by IKHC Ethics Committee with reference number 129908. One hundred and seventy seven patients, ASA I, II, III, and aged 50 years or older, scheduled for elective outpatient urologic surgeries, were enrolled. Individuals with a history of adrenal dysfunction, hemodynamic instability, and allergy to propofol or etomidate were excluded. Written informed consent was obtained from the patients or their surrogates. The performed urologic procedures included cystoscopy, placement or removal of double J stent, and biopsy. Patients' age, gender, weight, height and ASA class were recorded.

After intravenous (IV) cannulation with a 20-gauge cannula, patients were placed in the lithotomy position, a Ringer's solution was infused intravenously at a rate of 3-5 mL kg^{-1}, and oxygen was provided. Premedication with fentanyl 1 µg Kg^{-1} and midazolam 0.02 mg kg^{-1} was applied intravenously. Thereafter, the patients were randomly allocated to two groups: one etomidate group (88 patients) and one propofol group (89 patients). Randomization occurred through computer-generated randomization codes placed in opaque sealed envelopes by a person not involved in the study. In the etomidate group (E), an IV 0.1 mg kg^{-1} bolus dose of etomidate was administered, followed by 0.05 mg kg^{-1} every 3-5 minutes as needed. In the propofol group (P), 1 mg kg^{-1} of propofol was first administered intravenously, followed by 0.5 mg kg^{-1} every 3 minutes if necessary. In both groups, if the patients felt uncomfortable during the procedure, the same bolus doses of etomidate or propofol were administered irrespective of the moment of the previous dose. All urological procedures were performed by three surgeons, who were not informed about study groups and the content of the solutions administered to each patient.

Patients were monitored for non-invasive blood pressure (NIBP), electrocardiogram (ECG), heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2). Values were recorded before induction as baseline (T0), immediately after the first bolus anesthetic injection (T1), five and ten minutes after injection (T2 and T3, respectively), and before transfer to the post anesthesia care unit (PACU) (T4).

In this double blind study, both the patients and the evaluator were blinded to the type of intervention. All drugs were labeled and similar in appearance, as we used lipophilic etomidate and propofol. A trained nurse anesthetist collected all data.

Studied variables included pain at the injection site, myoclonus, need for assisted ventilation, nausea, vomiting, antiemetic medication administration in the PACU, duration of sedation (time between induction of sedation and transfer of the patient to the PACU), duration of surgery, recovery time (time between transfer of the patient to the PACU and full wakefullness), sedation score [Ramsay sedation scale (RSS)] intraoperatively and in the PACU, and pain score in the PACU. Pain was measured by a 0 to 10 scale, 0 representing no pain and 10 being the severest imaginable pain. Sedation scores according to RSS are as follows : 1 = anxious, agitated or restless ; 2 = cooperative, oriented and tranquil ; 3 = responds to commands only ; 4 = asleep, but with brisk response to light glabellar tap or loud auditory stimuli ; 5 = asleep, but sluggish response to light glabellar tap or loud auditory stimuli ; 6 = asleep, no response (8). Patients' satisfaction was assessed by a 0 to 10 visual analogue scale, and was evaluated regarding intraoperative comfort and pain experience. Anesthesiologists' and urologists' satisfaction was also assessed by the same scale with respect to patient management. Incidence of adverse effects was carefully observed, and appropriate intervention were performed. If myoclonus occurred, midazolam was administered. In case of apnea, head extension, placement of oral airway and bag-valve-mask ventilation were planned. The occurence of pain during intravenous injection of either etomidate or propofol was assessed by asking the patients. Any sensation of pain by the patient was considered as a painful injection. All patients were recommended to take vitamin C 500 mg daily for 3 days after the operation, based on our hospital protocol.

Statistical Analyses

In a pilot study of 10 patients in each group, considering the hemodynamic parameters as the primary outcome, power analysis was performed. The sample size in each group was then calculated as being 85, based on $\alpha = 0.05$ and $\beta = 0.2$.

Data were analyzed using the SPSS version 18 software (SPSS, Inc. Chicago, IL, USA). Normal distribution of samples was confirmed by a Kolmogorov-Smirnov test. Quantitative variables

were reported as mean ± SD and compared using a t-test or a Mann-Whitney U test. ANOVA for repeated measures was applied to analyze repetitive quantitative data. Qualitative variables were expressed as frequency and compared using a chi-square test. A P-value < 0.05 was considered to be statistically significant.

Results

One hundred and seventy seven patients entered the study, 88 patients in group E and 89 patients in group P. No drop out happened (Fig. 1). The groups were not different regarding patient characteristics (Table1).

Systolic, diastolic and mean arterial blood pressure were measured before induction, after induction, during the operation and in the PACU. The values were not different at baseline but there were significant differences between groups with respect to systolic, diastolic and mean arterial blood pressures at T1 to T4 (Fig. 2). However, the repeated measurement ANOVA showed that propofol induced a greater decrease in systolic, diastolic and mean arterial blood pressures (P-values < 0.01). The decreases in systolic, diastolic and mean arterial blood pressure were significant from T0 to T4 (time effect) (P-values < 0.001) (Fig. 2).

HR showed no significant difference between groups. RR was also similar with the exception of the time point before transfer to the PACU (T4), where propofol showed a lower RR (P-value < 0.001) (Table 2). The repeated measurement ANOVA showed no within group significant differences in RR.

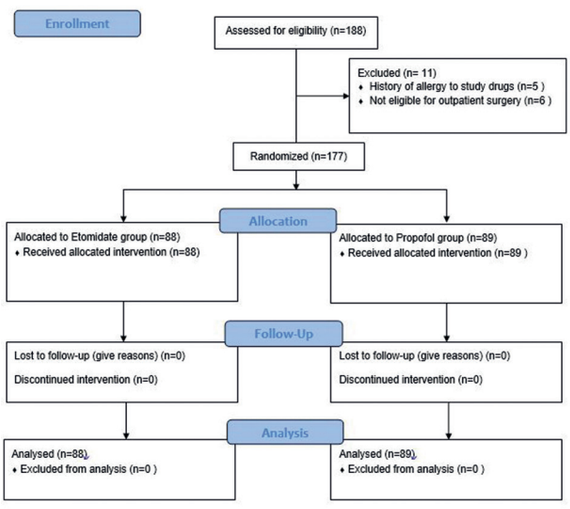

Figure 1. — The randomized trial flow diagram.

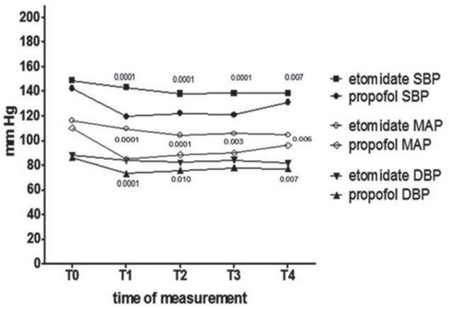

Figure 2. — Non-invasive blood pressure measurements at different time intervals. T0: baseline, T1: immediately after the first bolus anesthetic injection, T2: 5 minutes after injection, T3: 10 minutes after injection, T4: before transfer to the PACU. P-values < 0.05 are written on the chart.

Table 1

Patients' characteristics. Data are expressed as mean + (SD) or as number of patients (%)

	Propofol (n=89)	Etomidate (n=88)	P-value
Age (years)	61.4±10.1	62.4±11.0	0.47
Male Gender Female	63(70.8%) 26(29.2%)	72(81.8%) 16(18.2%)	0.08
Weight (Kg)	75.1±12.1	72.8±12.3	0.20
I ASA class II III	46 (51.7%) 31(34.8%) 12(13.5%)	50(56.8%) 28(31.8%) 10(11.4%)	0.48

SD : standard deviation.

Table 2

Heart rate (mean beat.min^{-1}± SD) and respiratory rate (mean breath.min^{-1} ± SD) at time intervals

		Propofol	Etomidate	P-value
T_0	RR	11.1±1.1	11.5±1.5	0.62
	HR	78.9±13.6	79.3±14.1	0.76
T_1	RR	10.6±.9	10.9±1.4	0.416
	HR	78.6±13.9	76.0±13.0	0.255
T_2	RR	10.6±1.1	10.8±1.0	0.435
	HR	75.5±12.7	74.3±13.9	0.501
T_3	RR	10.7±1	10.6±1	0.544
	HR	75.1±11.2	73.9±12.7	0.382
T_4	RR	10.2±.5	11.7±1.2	0.0001*
	HR	76.1±12.4	76.8±12.9	0.936

T : time, HR : heart rate, RR : respiratory rate, SD : standard deviation

Unlike RR, O_2 saturation showed significant differences between groups. After the injection of bolus doses of drugs, oxygen saturation dropped to 90.3% ± 9.4 in group P, while etomidate caused no such change (Fig. 3).

Incidence of side effects was recorded both during surgery and post-operatively until transfer

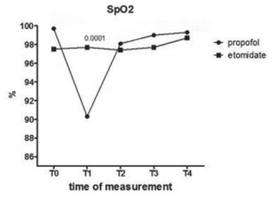

Figure 3. — Saturation of oxygen at time intervals. P-values < 0.05 are written on the chart.

Table 3

Incidence of side effects.
Data are expressed as number of patients (%)

Side effect	Propofol (n=89)	Etomidate (n=88)	P value
Pain at injection site	9(10.2%)	40(46%)	0.0001
Myoclonus	1(1.1%)	6(6.9%)	0.050
Post-op nausea	0	4(4.8%)	0.120
Post-op vomiting	0	2(2.4%)	0.145
Post-op antiemetic administration	0	2(2.4%)	0.145
Hypotension (MAP <30% baseline)	7(7.9%)	1(1.1%)	0.03
Bradycardia (< 30% baseline)	6(6.7%)	0	0.02
SpO2< 90%	55(61.8%)	18(20.5%)	<0.001
Need to assist ventilation	31(34.8%)	5(5.8%)	<0.001

to the ward. Apnea after the first bolus injection of the drug was observed in 37 patients (41.6%) of group P and one patient (1.1%) of group E (P-value 0.0001). Five minutes after injection, three patients of group P (3.4%) and one patient (1.1%) of group E developed apnea (P-value 0.317). No incidence of apnea was recorded at the other time points. Incidences of other side effects are listed in Table 3.

Other clinical data relevant to sedation are listed in Table 4. Duration of surgery and duration of sedation were similar in both groups. However, patients of group E stayed much longer in the PACU as compared to group P.

Patients, anesthesiologists and urologists' satisfaction were compared. When comparing the etomidate and propofol groups, no significant differences were observed in the satisfaction level of patients (median : 8 and 7, respectively) and urologists (median : 8 and 8, respectively). However, anesthesiologists' satisfaction was significantly higher in group E than in group P (median : 8 and 5, respectively; P-value 0.04)

Intraoperative RSS, RSS in the PACU and pain in the PACU were compared between the studied groups (Table 5). The only between-group significant difference concerned pain in the PACU (P-value 0.04).

Table 4

Comparison of some important variables between two groups.
Data are expressed as mean ± SD

	Propofol (n=89)	Etomidate (n=88)	P value
Induction time (minutes)*	6.1±1.4	6.4±1.3	0.17
Time of procedure (minutes)*	21.9±7.8	23.4±9.8	0.21
Recovery time (minutes)*	20.6±7.8	28.3±10.1	<0.001
Time to discharge (minutes)	188.1±55.2	200.5±58.3	0.15

(SD : standard deviation).

Table 5

Comparison of RSS and pain in PACU between propofol and etomidate groups. Data are expressed as median (Interquartile range).

	Propofol (n=89)	Etomidate (n=88)	P value
Intraoperative RSS	6(4-6)	6(4-6)	0.99
RSS in PACU	3(1-4)	3(1-4)	0.99
Pain in PACU	1(0-2)	2 (1-5)	0.04

RSS : Ramsay sedation scale, PACU : post anesthesia care unit.

Discussion

The hemodynamic effects of propofol and etomidate have been studied since their introduction in anesthesia practice. Early studies have shown that propofol causes a remarkable decrease in blood pressure without compensatory tachycardia. Its hypotensive effects are known to be similar to midazolam or barbiturates (9). This can be helpful during laryngoscopy and intubation, where tachycardia and increased blood pressure occurs. However, in elderly patients who suffer from cardiovascular diseases, hypotension can result in increased morbidity and mortality (10). The decrease in blood pressure depends on dose and infusion rate (11). A baseline mean arterial pressure <70 mmHg and age ≥50 years are other risk factors of hypotension in ASA class I and II patients (10). Unlike propofol, induction with etomidate has minimal effects on vascular resistance and blood pressure (11, 12). The cardiovascular effects of etomidate are mainly attributed to activation of the α2β adrenergic receptors of peripheral vascular smooth muscles, which results in vasoconstriction, and increased blood pressure (13). Due to its short onset and duration of action along with narrow side effect profile, etomidate has gained wide acceptability as an anesthetic agent for ambulatory procedures (14, 15).In the present study; we observed that the decrease in blood pressure was larger with propofol than with etomidate. This effect

began after the first bolus injection, and persisted until transfer of the patients to the PACU. Despite changes in blood pressure, HR was relatively constant in both groups. Although we detected a statistical difference in HR at T4 , this defference was not clinically relevant.

This is in accordance with previous studies, which reported little or no change in HR with propofol or etomidate (7, 16). Shah et al. reported a sustained increase in HR with propofol but not with etomidate (17). Hosseinzadeh et al. reported a decrease in HR after anesthesia with propofol and insertion of a laryngeal mask airway (LMA). They noted that, with etomidate, HR increased after the beginning of anesthesia but decreased after LMA insertion (12). Noteworthy, the doses of anesthetic agent used in these studies were different. This difference might account for different observations. The use of other anesthetic agents can also alter the results.

Apnea is commonly observed after induction of anesthesia with propofol, which can be aggravated by the concomitant use of an opioid (9). Although etomidate is known to spare respiratory function, Baude et al. have reported a decreased O_2 saturation with etomidate in patients undergoing short-time urologic procedures. This may be related to the higher bolus doses of etomidate that are needed for sedation. This higher dose of etomidate compared to our study could explain the higher incidence of hypoxemia, probably resulting from apnea or trismus (7). Data regarding the respiratory depressant effects of propofol are controversial. While some investigators reported no effect of propofol on RR and gas exchange (18), others have reported respiratory depression (19). We observed no significant difference in RR between the two groups, except at T4. Propofol and etomidate are both short-acting drugs with rapid elimination. No delayed respiratory effect has been reported for them. A possible explanation for this finding is the difference between pain scores in the PACU. Patients of group E rated higher pain scores in PACU and pain can result in increased RR.

The other studied side effects included pain at the injection site, myoclonus, as well as nausea and vomiting. Pain at the injection site and myoclonus are two common side effects of etomidate (14, 20, 21). In this study, pain at the injection site was significantly higher in group E than in group P. Some actions can be undertaken to reduce the incidence of this event, including water flush at the injection site, using lipid formulation, using lower doses, and injection into larger veins (22). Incidence of myoclonus was slightly higher in group E than in group P, but did not interfere with the surgical procedures. Reduction of dose and/or infusion rate and pretreatment with drugs such as fentanyl, midazolam or diazepam are suggested to reduce the incidence of etomidate-associated myoclonus (23, 24).

Incidence of nausea and vomiting and need for antiemetic administration was higher in group E than in group P, although the difference was not statistically significant. Propofol is known to have antiemetic properties, especially at subhypnotic doses (25). Nausea and/or vomiting are frequently reported as side effects of etomidate in some studies (15). However, more recently, the incidence of nausea after induction with etomidate in lipid emulsion was reported to be similar to the one of propofol, while the incidence of vomiting was higher with etomidate (26). Further investigations are needed to determine the association between etomidate and postoperative nausea. Patients' characteristics as well as drug doses and concomitant use of other sedatives may play a role in the incidence of postoperative nausea and vomiting.

In this study, patients of group E rated higher pain scores than those of group P. A few studies have suggested some analgesic effects of propofol (9, 24, 26), while etomidate lacks such property (26). Although this might explain lower pain perception in group P, it is worth noting that, in our study, patients receiving etomidate had longer surgeries and longer sedations compared with patients of the other group. This might reflect more invasive or complicated surgeries, that have caused more pain for the patients.

There are some other limitations to our study. The major one is that myoclonus resulting from etomidate could have interfered with proper blinding of the study. Another limitation is the method of administering the study drugs. We just used repeated bolus doses of propofol and etomidate for sedation, which can provoke more hemodynamic and respiratory adverse effects than a continuous infusion.

Conclusions

Our study demonstrate that both etomidate and propofol can induce satisfactory sedation in patients undergoing outpatient urologic surgeries. Despite the fact that hemodynamic and respiratory parameters were more stable when using etomidate, myoclonus and pain at the injection were more frequent with that medication.

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