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ORIGINAL ARTICLE

Propofol-Dexmedetomidine versus Ketamine-Midazolam in Obstructive Sleep Apnea Patients Undergoing Drug-Induced Sleep Endoscopy

Mohamed Magdy Yousef Ebrahim*, Zeinab Ebrahim Ahmed Alhossary, Amani Abdel-Azim Ali, Ezzat El-Shabrawi Galhom

Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author*
Mohamed Magdy Yousef Ebrahim

Email:
drmohamedmagdy@outlook.com

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ABSTRACT

Background: One of the most important factors in directing treatment strategies for obstructive sleep apnea is determining the location of blockage and the pattern of upper airway alterations during sleep which can be achieved by drug induced sleep endoscopy (DISE). For DISE, midazolam, propofol, and dexmedetomidine are the usually utilized sedatives. Therefore, it's important to understand which medication combination—propofol-dexmedetomidine or ketamine-midazolam—better simulates natural sleep and has fewer drawbacks when used in DISE. So, we aimed to compare between the efficacy and safety of propofol- dexmedetomidine and ketamine-midazolam in OSA patients undergoing DISE.

Methods: This prospective randomized double-blind clinical study was conducted at Anesthesia, Intensive Care and Pain management Department, Faculty of Medicine, Zagazig University Hospitals on OSA adult patients undergoing DISE. All Patients were randomly divided into 2 groups of 44 patients each. Patients were randomized and allocated either in (group PD) to receive a combination of propofol and dexmedetomidine or (group KM) to receive a combination of ketamine and midazolam. The primary outcome of the study was the number of procedures successfully completed in each group.

Results: the number of patients with successful completion of the procedure was 41 in group PD and 33 in KM group. Regarding sedation score, it was lower in PD group than KM group (P=0.00).

Conclusions: Both propofol-dexmedetomidine and ketamine-midazolam regimens can provide adequate sedation for OSA patients undergoing DISE. However, Propofol-Dexmedetomidine combination may be preferred for DISE offering efficacy and safety.

Keywords: Propofol, Dexmedetomidine, Ketamine, Midazolam, Drug-Induced Sleep Endoscopy.

INTRODUCTION

The condition known as obstructive sleep apnea (OSA) is common. Over 1 billion people worldwide suffer with obstructive sleep apnea in the 30- to 69-year-old age range [1].

The hallmark of this sleep-related breathing condition is recurring episodes of partial or total upper airway collapse, which, when occurring during sleep, last for at least ten seconds and are linked to decreased arterial oxygen saturation [2].

Although there are many treatment options for obstructive sleep apnea, the condition is still common and can be managed medically or through life style changes, Surgery involving soft tissues (tonsillectomy, supraglottoplasty) and realignment of the facial bone structure (maxillomandibular advancement and expansion)[3].

Finding the obstruction that is producing the apnea or hypopnea episodes is the cornerstone of OSA care. Drug induced sleep endoscopy is a procedure in which a patient is given a medicine to induce sleep while an endoscopy is being performed to observe the upper airway [4].The soft palate, the hypopharynx, the nasopharynx, the posterior oropharynx, and the nasal passages, and the supraglotti can dglotticair way sareall examined during the endoscopic examination. Itisalsopossibletoassessthetrachealairwayands ubglottis.Inordertoqualifyfor DISE, the patient must be in a state that closely resembles physiological sleep, breathing naturally through their native airway, and having oxygen desaturation values that are similar to those that occur during sleep[5].

DuringDISE,avarietyofsedativeswereemploye d,eithersinglyorincombination, to induce sedation. Midazolam, propofol, and dexmedetomidine arethe three sedatives that are most frequently used for DISE. Propofol is the most effective medication because of its pharmacokinetic profile, which enables a swiftonset and recovery from sedation. However, in individuals with OSA, propofol might result in respiratory depression, a decrease in ventilatory drive, and a loss of muscular tone[6].

A potential pharmacological substitute for DISE has been explored in the pastten years: Dexmedetomidine is a selective agonist of alpha-2 adrenergic receptors that resembles the normal sleep electroencephalogram (EEG) pattern without inducing respiratory depression [3,7]. The sedative mechanism of dexmedetomidine involves inhibition of the locus ceruleus (LC), which disinhibits ventrolateral preoptic nucleus (VLPO) firing. The sedative response is dependent on tuberomammillary nucleus (TMN) activity, which is inhibited by the increased release of gamma-aminobutyric acid (GABA) at the terminals of the VLPO [8].

Over a broad dose range, the respiratory stimulant ketamine eliminates theconnectionbetweenunconsciousnessandfail ureoftheupperairwaydilatormuscles.Incontrast topropofol,ketaminemayhelpmaintainairwayp atencyduring anesthesia and sedation but it is not devoid of complications [9].

Stages 1 and 2, which are stable non-rapid eye movement (NREM) sleep states, had the highest amount of time spent in midazolam sedation. One sedative that was first used in DISE and is still a good anesthetic for sleep endoscopy is midazolam [10]. Midazolam primarily exerts a dose-dependent depressive effect on respiration[11]. It may impair the protective airway reflexes, increasing the risk of upper airway obstruction. This is more common in sedated patients, particularly those in a supine position [12].

We hypothesized that there is a difference between propofol-

dexmedetomidine and ketamine-midazolam in providing better simulation of natural sleep and less complications in obstructive sleep apnea patients undergoing drug induced sleep endoscopy.

METHODS

Study Design:

88 adult male or female patients with obstructive sleep apnea undergoing drug-induced sleep endoscopy who had a BMI of less than 35 kg/m^2, a physical status of II or III according to the American Society of Anesthesiologists (ASA) and an age of 21-60 years old participated in this prospective, randomized, double-blind clinical investigation. The Anesthesia, Intensive Care, and Pain Management Department Faculty of Medicine, Zagazig University hospitals was the site of the study . It received approval from the Institutional Review Board (IRB number 10802-30-5-2023) of faculty of medicine Zagazig University. Exclusion criteria included pregnancy, congestive heart failure, seizures, cerebrovascular disease, moderate-to-severe chronic obstructive pulmonary disease or uncontrolled asthma, known drug allergies, anticipated difficult intubation, mental, neurological, or development aldisorders and patient refusal.

Two randomly selected groups of forty-four patients each were formed (Figure 1S).The ketamine-midazolam group and the other group were assigned to patients at random (group KM) or the group PD (propofol-dexmedetomidine) utilizing a computer-generated 1:1 ratio. The study anesthesiologist opened the sealed envelope containing the randomization assignments just before the surgery took place. The envelopes were sealed until the day of the procedure. All participating patients were interviewed preoperatively to explain the procedure and the possible risks. History was taken, physical examination and airway assessment were done and routine investigations were reviewed. Informed written consent was obtained. Patients were instructed to fast 6 hours for solids and 2 hours for clear fluid before the procedure. Ten minutes before induction of sedation, full monitoring including pulse oximetry, non-invasive arterial blood pressure & electrocardiogram were applied and basal readings were recorded. Two peripheral intravenous lines were inserted. Three - five drops of xylometazoline 0.1% were given in the nasal cavity of patients for endoscopy. All patients were preoxyegenated with 100% oxygen for 3 minutes before induction. None of the study patients received any sedative premedications.

Group PD (n=44): patients received intravenous infusion of dexmedetomidine (Precedex, Hospira, Egypt, 100 µg/ml) in 50 ml syringe (4 µg/ml) via a syringe pump loaded with 1 µg/kg over 10 minutes, then 1 µg/kg/hr of dexmedetomidine infusion and 1 mg/kg intravenous bolus of propfol (Diprivan, Astra Zeneca, Egypt) after loading dexmedetomidine and another syringe pump loaded with 1 mg/kg. Up to the very end of the process, both infusions were kept constant.

Each infusion in a separate IV line.

Group KM (n=44): Patients received ketamine (Ketam, Eipico, Egypt) 1 mg/kgas intravenous bolus followed by ketamine infusion of 1 mg/kg/hr via a syringepump& midazolam (Dormicum, Egyptian Pharmaceutical Trading Company,Egypt) 20 µg/kg as intravenous bolus followed by

midazolam infusion of 20µg/kg/hr using a different syringe pump. Up to the very end of the process, both infusions were kept constant. Each infusion in a separate IV line.

The MOAA/S sedation score was used to determine the patient's level of sedation once they began to snore (Table 1S) [13] and when the score was ≤ 2, the endoscopist passed a flexible fiberoptic endoscope via the nares to the nasopharynx. The scope then was passed through the nasopharynx into the oral cavity and hypopharynx to evaluate fixed and dynamic airway obstruction. The base of tongue and supraglottic structures were also examined.If there was aconcern about subglottic collapse, the endoscopist administered topicall ocalanes the siaand passed ascope through the vocal cord stoexamine the subglottis and trachea.

Patients in both groups were given fentanyl1 µg/kgonce when they moved during DISE. If the patient moved again, it was considered as inability to complete the procedure.

After the procedure general anesthesia was induced to start surgery.

Sample size: Assuming the frequency of successful procedures completed in 72% vs 96% in Propofol. Vs. Propofol-Dexmedetomidine group [14]. At 80% power and 95% CI, the estimated sample was 88 cases, 44 cases in each group using Open epi program.

Primary out come measurement was the number of procedure ssuccessfully completed in each group.

Secondary out come measurements included the following parameters: time to fall asleep, the degree of sedation measured using the MOAA/S (modified observer's assessment of alertness sedation) scale (Table 1S) [13] and satisfaction of surgeon which was assessed with the5-point Likert scale (Table2S) [15]. Before induction, when the patient fell unconscious, and every five minutes during the endoscopy, measurements of the peripheral oxygen saturation (SpO2), heart rate (HR), and mean arterial blood pressure (MAP) were taken.

Any complications were recorded and managed including hypoxia (SpO_2< 90%) particularly for patients with persistent desaturation or apnea ≥ 30 seconds, face mask ventilation was used along with head tilt, chin lift, or jaw thrust. Bradycardia (HR < 50 bpm) and it was managed with atropine 0.01 mg/kg, tachycardia (HR increased by > 25% from baseline) and/or elevated blood pressure (systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) increased by>25%frombaseline)were treated with fentanyl 1 µg/kg, intravenous crystalloids, and ephedrine 6 mg intravenous increments as needed, for hypotension (MAP dropped by more than 25% from baseline).

Statistical Analysis:

SPSS version 27 was used for all statistical analyses. Kolmogorov-Smirnov and Shiparo-Wilk tests were used to determine normality.Normallydistributedcontinuousdata wererepresentedasmeanandstandarddeviation. Independentsamplet test was used to normally distributed comparing the continuous data between both groups. Categorical data were represented as event and percentage. With regard to categorical data, comparisons between groups were made using the Fisher Exact or Chi-square tests. General linear model ormixed linearmodel were used for assessment of repeated measurements and to compare repeated measurements with

baseline within the same group.

RESULTS

Regarding the characteristics of the patients who were included and the procedure's duration, there was no statistically significant difference (p>0.05) (Table3S). Regarding successful completion of procedure, it was higher in PD group (93.20%) than KM group (75.00%) (p=0.039) (Table 1).

Regarding time to fall a sleep (measured by a stop watch), it was 22.65 ± 4.67 seconds in PD group and34.47±5.33 in KM group, with statistically significant difference between both groups (P=0.00). Regarding sedation score, it was significantly lower in PD group than KM group(P=0.00) (Table 2).

Regarding HR ,after administration nof medicines, the PD group experienced a large HR decrease, while the KM group experienced a significant HR increase. Following medication delivery, repeated HR measurements revealed a statistically significant difference between the two groups. (P=0.00) (Table 3). Regarding MAP, after administration ofdrugs, there was a significant MAP decrease in PD group and a significant MAPincrease in KM group. Following medication administration, repeated MAP measurements revealed a statistically significant difference between the two groups (P=0.00)(Table4).RegardingSpO_2,between the two groups, there was no statistically significant difference(P>0.05). Intraoperative SpO_2 stability was higher in KM group (Table5).

Regarding surgeon satisfaction, it was higher in PD group(4.32±0.58) than KM group (2.81±0.62) (p=0.00)(Table 6). Regarding complications, there were no statistically significant difference between both groups (Table 7).

Table1: Successful completion of procedure in both groups

Successful completion of procedure	PD group	KM group	P value
no	3 (6.80%)	11(25.00%)	**0.039**
yes	41(93.20%)	33(75.00%)	

Qualitative data were expressed as event (percentage),Cross-tabulation and exact fisher test, P value was considered significant if <0.05.

Table2: Timetofallasleep (seconds)and sedations core in both groups

	PD group (44)	KM group (44)	Mean Difference	P value
	Mean ± SD	Mean ± SD		
Time to fall asleep (seconds)	22.65±4.67	34.47±5.33	-11.822	**0.000**
Sedation score	1.30±0.594	2.02±0.628	-0.727	**0.000**

Quantitative data were expressed as mean ± SD, Independent sample-t test; P value was considered significant if <0.05.

Table3: Heart ratemeasurementsinbothgroups (beat/min)

HR (beat/min)	**PD group (44)**	**KM group (44)**	**Mean Difference**	**P value**
Baseline	80.45±7.68	82.70±8.54	-2.254	0.196
On falling a sleep	72.43±4.70	91.59±3.80*	-19.157	**0.000**
After5 minutes	72.34±4.81	89.70±3.60*	-17.359	**0.000**
After10 minutes	67.73±6.07	105.05±9.46*	-37.323	**0.000**
After15 minutes	60.09±8.02	113.77±12.95*	-53.681	**0.000**
After20 minutes	60.90±7.28	110.13±11.02*	-49.233	**0.000**
After25 minutes	60.90±7.28	110.20±8.92*	-49.310	**0.000**
After30 minutes	59.81±7.82	109.22±8.99*	-49.409	**0.000**
On falling a sleep versus baseline	**0.001**	**0.000**		
After5minutesversus baseline	**0.000**	**0.000**		
After10minutesversus baseline	**0.000**	**0.000**		
After15minutesversus baseline	**0.000**	**0.000**		
After20minutesversus baseline	**0.000**	**0.000**		
After25minutesversus baseline	**0.000**	**0.000**		
After30minutesversus baseline	**0.000**	**0.000**		

Quantitative data were expressed as mean ± SD, MD: mean difference, P value was considered significant if < 0.05; Mixed linear model

Table4 : Mean arterial pressure measurements in both groups (mmHg)

MAP (mmHg)	**PD group**	**KM group**	**Mean Difference**	**P value**
Baseline	85.52±6.75	84.09±6.82	1.429	0.326
On falling asleep	77.93±3.66	86.50±5.37*	-8.570	**0.000**
After 5 minutes	78.22±3.78	88.69±6.89*	10.469	**0.000**
After 10 minutes	78.88±5.18	90.54±4.63*	11.661	**0.000**
After 15 minutes	77.83±6.83	89.56±7.22*	11.734	**0.000**
After 20 minutes	74.84±4.89	90.73±8.25*	15.887	**0.000**
After 25 minutes	74.54±4.67	96.08±9.06*	21.538	**0.000**
After 30 minutes	74.66±4.63	93.67±9.76*	19.019	**0.000**
On falling asleep versus baseline	**0.000**	1.000		

MAP (mmHg)	PD group	KM group	Mean Difference	P value
After 5 minutes versus baseline	**0.001**	0.336		
After 10 minutes versus baseline	**0.000**	**0.008**		
After 15 minutes versus baseline	**0.000**	**0.021**		
After 20 minutes versus baseline	**0.000**	**0.000**		
After 25 minutes versus baseline	**0.000**	**0.000**		
After 30 minutes versus baseline	**0.000**	**0.000**		

Quantitative data were expressed as mean ± SD, MD: mean difference, MAP: mean arterial pressure. P value was considered significant if<0.05; Mixedlinearmodel

Table5: Oxygen saturation measurements (%)in both groups

SpO_2 (%)	PD group	KM group	MD	P value
Baseline	96.76±5.03	95.86±4.71	0.904	0.387
On falling asleep	95.24±2.18	94.96±2.42	0.281	0.570
After 5 minutes	95.09±3.90	94.76±4.07	0.327	0.702
After 10 minutes	92.72±2.16	93.60±2.05	-0.878	0.054
After 15 minutes	94.12±3.12	93.38±2.94	0.746	0.252
After 20 minutes	92.33±2.29	91.86±2.52	0.472	0.361
After 25 minutes	93.10±2.54	93.54±3.20	-0.443	0.473
After 30 minutes	93.91±2.81	94.21±2.56	-0.300	0.639
On falling asleep versus baseline	1.000	1.000		
After 5 minutes versus baseline	1.000	1.000		
After 10 minutes versus baseline	**0.001**	0.156		
After 15 minutes versus baseline	0.106	**0.048**		
After 20 minutes versus baseline	**0.000**	**0.000**		
After 25 minutes versus baseline	**0.004**	0.219		
After 30 minutes versus baseline	**0.010**	0.351		

Quantitative data were expressed as mean ± SD, MD: mean difference, P value was considered significant if<0.05; Mixedlinearmodel

Table6: Surgeonsatisfactioninbothgroups.

	PD group	KM group	MD	P value
Surgeon satisfaction	4.32±0.58	2.81±0.62*	1.510	**0.000**

Quantitative data were expressed as mean ± SD, MD :mean difference, Pvalue was considered significant if<0.05;Independentsample-ttest

Table7: Complicationsinbothgroups

	PD group	KM group	P value
Hypotension	2 (4.50%)	0 (0.00%)	0.493
Hypertension	0 (0.00%)	3 (6.80%)	0.2414
Tachycardia	0 (0.00%)	2 (4.50%)	0.493
Bradycardia	2 (4.50%)	0 (0.00%)	0.493
Oxygendesaturation<90%	5(11.60%)	9(20.50%)	0.383

Qualitative data were expressed as event (percentage),Cross-tabulation and exact fisher test, P value was considered significant if <0.05.

DISCUSSION

The current study's findings showed that employing propofol and dexmedetomidine together was linked to a higher percentage of procedure completion success, lower sedation score and shorter time to fall asleep than using a combination of ketamine and midazolam.

Regarding time to fall asleep and sedation scores in our study, a shorter timeto sleep (22.65 ± 4.67 seconds vs. 34.47 ± 5.33 seconds) and statistically significant reduced sedation levels with the PD group in comparison to the KM group. When taken combined, propofol and dexmedetomidine appear to sedate patients more swiftly and efficiently, which is helpful for DISE operations.

Thisfindingisinconsistentwith[16]discovered that the ketamine group (which received a 1.0 mg/kg IV bolus of ketamine over 10 s followed by the infusion rate of 1 mg/kg/hr to the end of DISE) was not as well-treated as the dexmedetomidine group (which received a 1 µg/kg bolus of dexmedetomidine over 10 min) experienced superior sedative quality and aquicker timet of all a sleep. Intravenous midazolam0.1mg/kgwas administered to both groups.

Another study using dexmedetomidine (10 minutes at 1.0 µg/kg, then 0.2–1.4 µg/kg/hour) revealed that half of the patients did not receive enough sedation, necessitating the injection of propofol in this group [10]. Adding propofol to dexmedetomidine in our study might enhance the onset of sleep in our study.

Regarding HR and MAP in our study, repeated assessments revealed that the PD group's heart rate and mean arterial pressure significantly decreased, while these metrics increased in the KM group. Propofol and dexmedetomidine have sympatholytic action that might result in bradycardia and hypotension, which is probably why there is this difference [17]. On the other hand, ketamine's sympathomimetic effects are known to raise blood pressure and heart rate [18].

This partially agrees with Abdelgalel [14] who sought to determine whether, in comparison to propofol alone (Group P received propofol loading dose of 0.5 mg/kg over 3 min then continuous infusion in a dose of 25–75 mcg/kg/min), the addition of dexmedetomidine to propofol (Group PD received propofol infusion as group P and dexmedetomidine intravenous infusion with a loading dose of 0.5 mcg/kg over 5 min then continuous infusion in a dose of 0.2–0.7 mcg/kg/h) could enhance the rate of procedures successfully completed and reduce the complications during drug-induced sleep endoscopy in patients with obstructive sleep apnea. He stated that there was no discernible change in the mean artery pressure (MAP) between the two groups. After commencing the investigated medications five minutes later and continuing the drug infusion for thirty minutes later, group PD's heart rate was noticeably lower than group P's heart rate.

Inagreement,Kimetal.[19]discoveredthatu

singdexmedetomidinegreatlyincreasedtherisk ofbradycardia.Becauseofitssympatholyticprop erties,dexmedetomidinecancausebradycardia[20].

Nelsonetal.[8] discovered that dexmedetomidine may result in significant hemodynamic instability, particularly bradycardia and hypotension. This may be related to the fact that dexmedetomidine-induced sedation is causally caused by endogenous sleep pathways; the sedative mechanism of dexmedetomidine involves inhibition of the locus ceruleus, which disinhibits VLPO firing. The sedative response is dependent on tuberomammillary nucleus activity, which is inhibited by the increased release of GABA at the terminals of the VLPO.

Viana et al. [21] evaluated and contrasted the effects on the bispectral index of midazolam, propofol, and dexmedetomidine (BIS), lowest SpO_2, and DISEfindings in the same patient population. One patient had bradycardia that wasclinically significant, based on their report. Prior reports of this effect during DISE with dexmedetomidine alone [22]and in relation to remifentanil[10].

RegardingSpO_2inourstudy,duringtheDISEmet hod,nodiscernibledifferencewasseenbetweent hetwogroups.Thisresultimpliesthattherespirato ry safety offered by both sedation procedures was satisfactory, which is important forOSApatientsundergoingDISE.Itwasobserve dthatagreaterproportionofpatientsin the KM group (20.5% vs. 11.6%) had oxygen desaturation below 90%; however, this difference did not reach statistical significance.

In agreement, Abdelgalel [14] found that there was no discernible differencebetween the two groups' lowest oxygen saturation or oxygen desaturation of lessthan90%.

Yongpingetal. [16] revealed that there was no discernibleoxy gende saturation with either ketamineordexmedetomidine.

Regarding the rate of successful procedure completion in our study,the PD group's rate was greater than that of KM group (93.2%versus 75%). This finding might be explained by the PD protocol's higher-quality anesthesia, which might make it easier to see the upper airway during theDISEprocess.

In agreement, Abdelgalel [14] revealed that group PD had a substantiallyhigherprobabilityofsuccessfulpro cedurecompletion(96%)thangroupP(72%).

In disagreement, Yongping et al. [16] revealed that, with a p-value of 0.008,the group utilizing Ketamine (Group K) had a substantially greater DISE successrate at 100% (43/43) than the group using Dexmedetomidine (Group D), at 85.11%(40/47).

Regarding surgeon satisfaction in our study, In contrast to the KM group, itwas higherinthe PDgroup.

This agrees with Abdelgalel[14] who stated that group PD surgeons atisfaction was noticeably higher than group P's. Surgeon satisfaction with group PD was better because of a reduced rate of coughing and gag reflexes, fewer process interruptions, and a higher rate of operation completion.

We found no statistically significant difference in the incidence of problems between the two groups in our investigation.

This agrees with Abdelgalel [14] who stated that there was no discernibledifference between the groups under study.

Conclusion:

This investigation showed that ketamine-midazolam and propofol-dexmedetomidine regimens are accepted for simulating natural sleep in OSA patients undergoing DISE. However, propofol-dexmedetomidine combination may be the preferred choice for DISE offering both efficacy and safety. The propofol-dexmedetomidine group showed shorter time to sleep, lower sedation scores, stable hemodynamics, higher surgeon satisfaction and a higher rate of successful procedure completion with comparable complication rates.

Limitations include relatively small sample size, the study was conducted at a single center, lack of follow-up, and blood level of the studied drugs was not measured.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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CONSORT
TRANSPARENT REPORTING of TRIALS

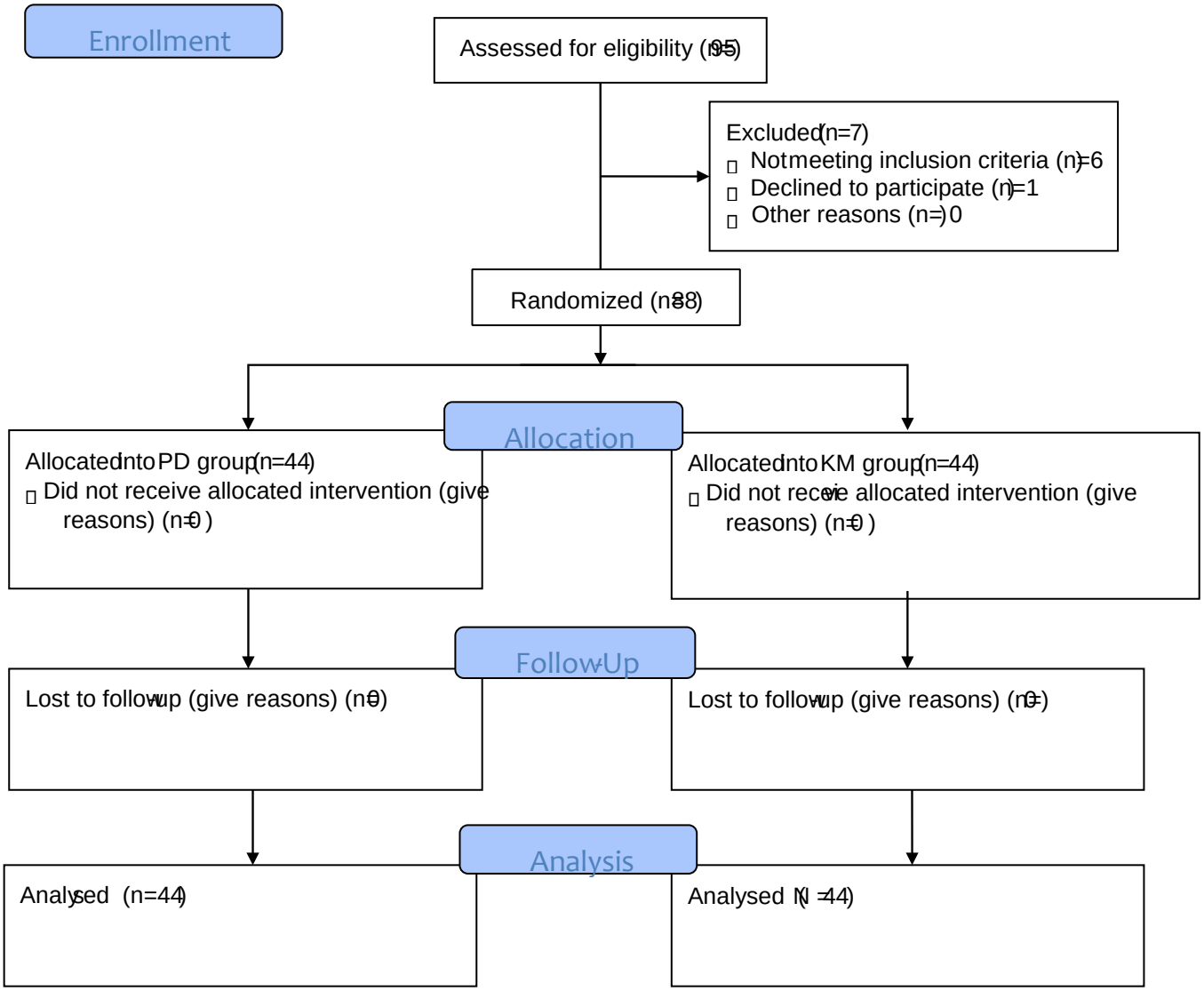

Table1S: Modified observer's assessment of alertness sedation (MOAA/S)scale**[13]**

Score	Responsiveness
6	Agitated
5	Responds readily to name spoken in normal tone(alert)
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/ or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to deep stimulus

Table2S: Likert scale**[15]**.

1	2	3	4	5
Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied

Table3S: Charactersofincludedpatientsandtimeofprocedure (minutes) in both group

Variables	**PD group**	**KM group**	**Test value**	**P value**
	Mean ± SD	Mean ± SD		
Age (years)	44.20±7.80	43.69±11.53	MD= 0.51٤	0.807
BMI (kg/m^2)	26.92±6.18	27.01±5.30	MD= 0.088	0.943
Time of procedure (minutes)	31.12±2.01	31.92±1.93	MD= -0.805	0.059
	N(%)	N(%)		
Gender				
male	35 (79.5%)	32(72.7%)	X^2=0.563	0.618
female	9(20.5%)	12(27.3%)		
ASA				
Grade II	37(84.1%)	35(79.5%)	X^2= 0.306	0.78
Grade III	7(15.9%)	9(20.5%)		

Quantitative data were expressed as mean ± SD, Qualitative data were expressed as event (percentage), independent sample-t test; cross-tabulation and chi-square test (X^2), MD: mean difference, SD :standard deviation, P value was considered significant if <0.05.

Citation:
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