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Ketofol Provides Better Upper Airway Size than Ketamine and Propofol in Pediatric Population Receiving Sedation for Magnetic Resonance Imaging

Ketofol Manyetik Rezonans Görüntüleme İçin Sedasyon Alan Pediatrik Hastalarda Ketamin ve Porofole Göre Daha Geniş Havayolu Açıklığı Sağlar

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ABSTRACT Objective: The present study aimed to compare the upper airway dimensions as well as hemodynamic and anesthetic features of propofol, ketamine, and ketofol in children undergoing magnetic resonance imaging (MRI) scanning. **Material and Methods:** This retrospective study was carried out on data derived from a total of 89 patients aged between 1-160 months who were allocated in 3 groups concerning the anesthetic agents administered during sedation for MRI. Group I received ketamine and propofol (ketofol), whereas Group II had propofol and, and Group III received ketamine in this procedure. **Results:** The cross-sectional area of the upper airway at the levels of the base of tongue, soft palate and epiglottis were higher in patients receiving ketofol, compared to those receiving propofol or ketamin ($p<0.05$). The duration of the recovery and total duration of the procedure were also significantly lower in patients receiving ketofol compared to others ($p< 0.001$). Systolic, diastolic, and mean blood pressures were significantly lower in children receiving propofol compared to those receiving ketamine or ketofol. **Conclusion:** Ketofol, which is the combination of ketamine and propofol, provides an effective and safe anesthetic regimen for magnetic resonance imaging in the pediatric population. Our results show that ketofol-based sedation also provides a larger upper airway size without the development of any hemodynamic derangement.

Keywords: Child; upper airway; sedation; ketofol; magnetic resonance imaging

ÖZET Amaç: Bu çalışma, manyetik rezonans görüntüleme (MRG) için sedasyon alan pediatrik hastalarda propofol, ketamin ve ketofolün hava yolu açıklığı, hemodinamik ve anestetik sonuçlar üzerine etiklerini karşılaştırmayı amaçlamaktadır. **Gereç ve Yöntemler**: Bu retrospektif çalışma MRG için 3 ayrı anestetik ajan ile sedasyon uygulanan, 1-160 ay arasında 89 hastanın verileri kullanılarak gerçekleştirilmiştir. Grup 1 ketamin ve propofol kombinasyonu olan ketofol, Grup 2 propofol, Grup 3 ise ketamin ile sedatize edilmiş hastalardan oluşmaktadır. **Bulgular:** Ketofol alan hastalarda propofol veya ketamin alanlara göre üst solunum yolu kesitsel alanı dil kökü, yumuşak damak ve epiglottis seviyelerinin tamamında daha genişti ($p < 0,05$). Derlenme süresi ve toplam prosedür süresi de ketofol grubunda diğer gruplara göre anlamlı olarak kısaydı ($p< 0,001$). Propofol uygulanan hastalarda işlem boyunca sistolik, diyastolik ve ortalama arter basınçları ketamin ve ketofol gruplarına göre önemli derecede düşüktü. **Sonuç:** Ketamin ve propofolün kombinasyonu olan ketofol MRG için sedasyon alan pediatrik hastalarda etkin ve güvenli sedasyon sağlar. Çalışmamızın sonuçları ketofol ile sedasyonun hemodinamik bozulmaya neden olmadan daha geniş hava yolu açıklığı sağladığını göstermektedir.

Anahtar Kelimeler: Çocuk; üst solunum yolu; sedasyon; ketofol; manyetik rezonans görüntüleme

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Deep sedation or anesthesia is frequently required for children scheduled for magnetic resonance imaging (MRI) to facilitate the completion of the scan. Sufficient depth of anesthesia may provide the cessation of movement during the procedure and diminish the anxiety resulting from the scanner medium.[1] Various anesthetic protocols have been utilized in children to avoid motion during MRI scanning, including ketamine, propofol, and midazolam.[2] However, airway obstruction to some degree during MRI examination has been demonstrated in a considerable proportion of spontaneously breathing neonates and infants.[3] Moreover, agents used for sedation of children might impend airway patency and seldom lead to total airway obstruction.[4] Identification of the ideal combination of anesthetic drugs during imaging procedures in children is therefore important. The combined use of anesthetic agents is advantageous since it allows the achievement of additional, positive, and complementary effects of the drugs. In this respect, it is possible to use lower doses to be given when used alone to avoid side effects that may occur with dose escalation.[5]

Propofol is a hypnotic drug with a rapid onset and short duration of action. Propofol has a narrow safety margin for its effects on respiratory functions. It has antiemetic action; however, it may display dose-related side effects such as bradycardia, hypotension, and respiratory depression.[5] Ketamine has analgesic features, and it can be used in conjunction with other drugs in general anesthesia or sedation. When combined with ketamine, propofol can be used at lower doses. Thus, its respiratory depressant effects can be omitted. On the other hand, the sympathomimetic effects of ketamine may counteract the depressive hemodynamic impacts of propofol. Moreover, analgesic effects of ketamine may diminish the requirement for additional analgesics.[6,7] In recent years the combination of ketamine and propofol called 'ketofol' rendered attention for various anesthetic procedures.[8] The synergistic effect of the two drugs and the resultant smoother sedation made ketofol favorable for use in several minor surgical procedures such as dental treatment or laser procedures.[9,10]

Our purpose was to compare the upper airway dimensions as well as hemodynamic and anesthetic features of propofol, ketamine, and ketofol in children undergoing MRI scanning.

MATERIAL AND METHODS

STUDY DESIGN

This retrospective study was carried out by using data derived from the medical records of 89 pediatric patients aged between 1-160 months who underwent MRI scanning in the pediatric radiology department of our tertiary care center between November 2018 and February 2019. Written informed consent was obtained for all subjects. The study was approved by the institutional review board and was performed in accordance with the most recent version of Helsinki Declaration (KEAK No: 2018/09, Date: 09/10/2018).

Patients were allocated into three groups according to the anesthetic protocol employed for sedation during scanning. In this context, Group I (n=31) received ketamine and propofol (ketofol), whereas Group II (n=30) had propofol, and Group III (n=28) had ketamine. The average age of our series was 4.85±3.32 years.

Baseline descriptives [age, gender, body mass index (BMI)], upper airway pathologies, adenotonsillar hypertrophy, Mallampati, and American Society of Anesthesiologists (ASA) scores, as well as patient and physician (radiologist and anesthesiologist) satisfactions, were recorded. Imaging was carried out on a 1.5-T whole-body system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). After MRI examination, image processing on a joined workstation using SYNGO (Siemens Medical Solutions) software was analyzed by two investigators experienced in pediatric MRI examination blinded to the study protocol and the imaging indications (the radiologists analyzing the measurements were blinded to whether the indication for MRI was a traumatic injury, which almost always requires NS or any other suspected intracranial pathology). Measurements of AP and transverse dimensions and CSA were performed to determine the upper airway size at three distinct levels: soft palate (SP), base of tongue (BOT), and the tip of the epiglottis (Figure 1, Figure 2, Figure 3). Systolic, diastolic, and mean arterial pressures, respiratory and pulse rates were

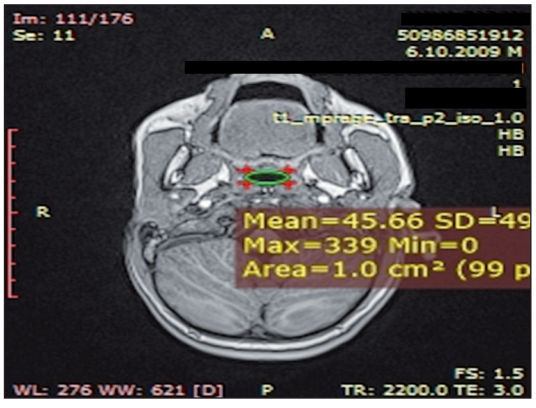

FIGURE 1: Measurement of upper airway dimension at the level of nasopharynx.

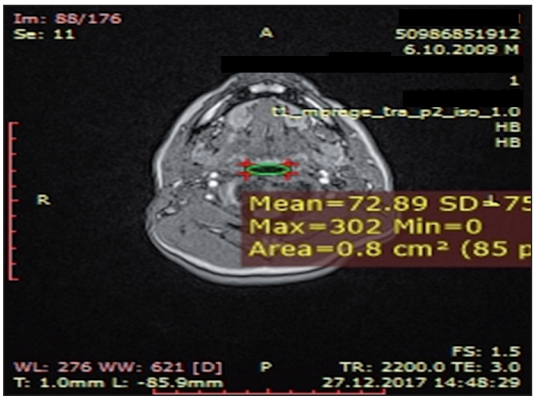

FIGURE 2: Measurement of upper airway dimension at the level of oropharynx.

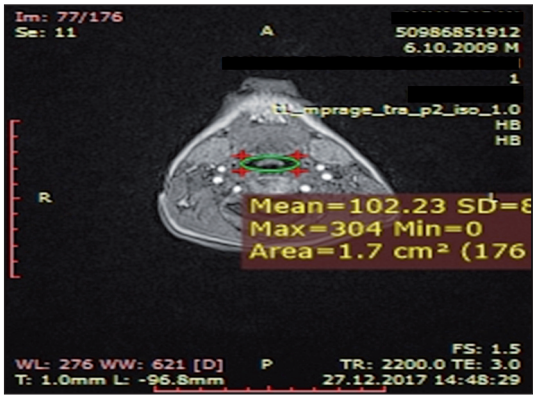

FIGURE 3: Measurement of upper airway dimension at the level of hypopharynx.

recorded before the induction of anesthesia and at various time intervals after the induction of anesthesia. The total duration of anesthesia and recovery time were noted.

The participants consisted of 44 females (49.4%), and 45 (50.6%) females (ASA physical status I-III). Exclusion criteria were as follows: a history of allergy to ketamine, propofol or midazolam; obesity (BMI ≥35 kg/m^2); or cardiac, pulmonary, hepatic, renal, and psychiatric disorders.

Following the provision of an intravenous line, intravenous midazolam 0.1 mg/kg was administered 3 min before the procedure. Propofol (10 mg/ml, target dose of 1 mg/kg iv.), ketamine (10 mg/ml, target dose of 1 mg/kg iv.), or ketofol (ketofol was prepared as a 1:1 mixture of ketamine 10 mg/ml and propofol 10 mg/ml mixed in a 20-ml syringe) was administered slowly (2 mL/10 s) until the patient no longer responded to his/her name being called loudly and showed loss of the eyelash reflex. Additional doses (10 mg ketamine for ketamine group, 10 mg propofol for propofol group and 5 mg ketamin + 5 mg propofol for ketofol group) were administered in 10-mg increments if the responsiveness to verbal command had not been lost within 60s after drug administration in each group. All subjects received %100 nasal oxygen throughout the sedation. All sedation procedures were carried out by the same anesthesiologist.

Non-invasive baseline measurements were made for blood pressure, pulse rate, and oxygen saturation. All vital sign values were recorded at intervals of 5 minutes during scanning. Monitorization involved heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and peripheral oxygen saturation. The side effects, such as desaturation, apnea, technical failure, nausea, and vomiting were questioned.

The recovery time was defined as the duration between sedation termination time and patient response time to the verbal command 'open your eyes'. Patients were discharged to the ward after stabilization of their vital signs and after the achievement of orientation with a complete return of motor function.

The satisfaction of the radiologist and family was evaluated using a visual analog scale of 3 sections: 1: good; 2: moderate; 3: poor. Anesthesiologist satisfaction was assessed as yes (satisfied) or no (unsatisfied).

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences version 21.0 program (*SPSS Inc., Chicago, USA*) was used for data analysis. Descriptive variables were expressed as mean ± standard deviation or median (minimum-maximum values) for continuous variables regarding the normality and as frequency (percentage) for categorical variables. The comparison of groups for means of two variables was performed by using Student's T-test or Mann-Whitney U tests. Comparison of three groups in terms of continuous variables was carried out via one-way analysis of variance (ANOVA) when the variables were distributed normally. Posthoc analysis was performed with the Tukey test. If the distribution of the data was not normal (age), comparison of the three groups was performed with the Kruskal Wallis test. Categorical variables were compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

TABLE 1: Comparison of 3 groups in terms of baseline descriptives and clinical parameters under investigation (Data are expressed as mean ± standard deviation).

	Group			
	Ketofol (n=31)	Propofol (n=30)	Ketamine (n=28)	p-value
Age, months	18 (1-120)	36 (4-160)	34 (2-148)	0.618
Body-mass index, kg/m²	16.29 5.02	16.42 5.27	15.4 4.59	0.818
Gender / Female	14 (45.2%)	16 (53.3%)	14 (50.0%)	0.814
ASA				
I	3 (9.7%)	4 (13.3%)	5 (17.9%)	
II	14 (45.2%)	13 (43.3%)	14 (50.0%)	
III	14 (45.2%)	13 (43.3%)	9 (32.1%)	
Mallampati score	2.55 0.81	2.53 0.68	2.61 0.63	0.857
OSAS, n	3 (9.7%)	0 (0.0%)	2 (7.1%)	0.112
Craniofacial anomaly, n	7 (22.6%)	3 (10.0%)	5 (17.9%)	0.400
Macroglossia, n	1 (3.2%)	0 (0.0%)	1 (3.6%)	0.433

ASA: American Society of Anesthesiologists;
OSAS: Obstructive sleep apnea syndrome; VAS: Visual analogue scale;
*: Statistically significant; N/A: not applicable.

RESULTS

The comparison of baseline descriptive, clinical and anesthetic parameters are presented in Table 1. There were no significant differences between 3 groups in terms of age, BMI, gender distribution, American Society of Anaesthesiologists' (ASA) scores, Mallampati scores, adenotonsillar hypertrophy, macroglossia and desaturation.

TABLE 2: Comparison of upper airway dimensions at the levels of epiglottis, soft palate and tongue base and durations of sedation in 3 groups under investigation.

	Groups			
	Ketofol (n=31)	Propofol (n=30)	Ketamine (n=28)	p-value
Epiglottis				
Anteroposterior, mm	10.68 2.46 [a]	9.18 2.83 [b]	8.97 3.09 [b]	0.047
Transverse, mm	16.09 3.34	12.42 3.27	13.35 3.56	0.558
Cross-sectional area, cm²	1.48 0.51 [a]	1.17 0.44 [b]	1.23 0.66 [b]	0.048
Tongue base				
Anteroposterior, mm	9.82 2.70	8.75 2.69	8.47 4.15	0.126
Transverse, mm	12.06 3.07	10.46 2.51	10.53 3.48	0.212
Cross-sectional area, cm²	1.16 0.41 [a]	0.87 0.34 [b]	0.92 0.48 [b]	0.033
Soft palate				
Anteroposterior, mm	6.39 1.97	5.21 2.49	5.43 2.6	0.542
Transverse, mm	12.64 3.49	11.70 4.24	11.33 3.87	0.558
Cross-sectional area, cm²	0.83 0.39 [a]	0.66 0.42 [b]	0.68 0.40 [b]	0.048
Duration, min				
MRI scanning	23.13 4.94	22.33 5.68	24.25 8.35	0.224
Recovery	86.22 28.09 [a]	119.67 4.56 [b]	123.32 3.45 [b]	<0.001
Total	111.11 30.14 [a]	144.96 7.52 [b]	150.94 10.76 [b]	<0.001

MRI: Magnetic resonance imaging. [a,b] = The same letter in the same row indicates lack of statistical significance between the groups marked with the same letter.

Data concerning the upper airway size in the three groups are given in Table 2. The cross-sectional area of the upper airway at the levels of BOT, soft palate and epiglottis were larger in patients receiving ketofol, compared to those receiving propofol or ketamin separately. The duration of the recovery and total duration of the procedure were also significantly shorter in patients receiving ketofol compared to others.

Analysis of hemodynamic and respiratory parameters yielded that the change in systolic, diastolic and mean blood pressures, and in respiratory rate and sPO_2 from baseline to the 20th minute of the procedure were similar in all groups. However, the hange in heart rate from baseline to the 20th minute of the procedure was significantly lower in ketamine group ot the ketofol and propofol groups (Table 3).

The incidences of insufficient sedation, technical failure, and nausea and vomiting were also similar in 3 groups. The satisfaction level of the anesthesiologists was not different in 3 groups under investigation. The satisfaction levels of the radiologists and families could not be statistically assessed due to the small number of samples in some subgroups (Table 4).

TABLE 3: Comparison of hemodynamic and respiratory variables in 3 groups.

	Group			
	Ketofol (n=31)	Propofol (n=30)	Ketamine (n=28)	p value
ΔSBP, mmHg	9 (-34-56)	8 (-25-57)	1.5 (-39-33)	0.430
ΔDBP, mmHg	4 (-38-53)	7.5 (-18-53)	1 (-27-39)	0.285
ΔMBP, mmHg	2 (-43-44)	9.5 (-29-53)	6 (-19-33)	0.395
ΔHR, min	6 (-30-37)[a]	1.5 (-9-21) [a]	-7 (-46-20) [b]	<0.001
ΔRR, min	0 (-5-10)	0 (-5-7)	0 (0-5)	0.981
ΔspO_2, %	0 (0-10)	0 (-3-5)	0 (0-3)	0.238

Data are presented as median (min-max).
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; HR: Heart rate; RR: Respiratory rate; spO_2: oxygen saturation. Δ: The difference between baseline and 20th minute measurements (baseline-20th minute value) [a,b] = The same letter in the same row indicates lack of statistical significance between the groups marked with the same letter.

TABLE 4: Complication rate and outcomes.

	Ketofol (n=31)	Propofol (n=30)	Ketamine (n=28)	p value
Desaturation, n	2 (6.5 %)	0 (0.0%)	2 (7.1)	0.183
Apnea, n	1 (3.2%)	0 (0.0%)	0 (0.0%)	0.345
Insufficient sedation, n	5 (16.1%)	3 (10.0%)	9 (32.1%)	0.088
Technical failure, n	5 (16.1%)	1 (3.3%)	5 (17.9%)	0.126
Nausea-vomiting, n	1 (3.2%)	0 (0.0%)	2 (7.1%)	0.224
Satisfaction of the anesthesiologist, n	29 (93.5%) 30 (100.0) 28 (100.0%) 0.116			
Satisfaction of the radiologist, n	27 (87.1%)			
1	from baseline to the	29 (96.7%)	17 (60.7%)	
2	from baseline to the 20th	1 (3.3%)	3 (10.7%)	<0.001
3	minute of the procedure	0 (0.0%)	8 (28.6%)	
	were 4 (12.9%) 0 (0.0%)			
Satisfaction of the family, n				
1	22 (71.0%)	26 (86.7%)	24 (85.7%)	
2	8 (25.8%)	3 (10.0%)	1 (3.5%)	0.082
3	1 (3.2%)	1 (3.3%)	3 (10.7%)	

DISCUSSION

We aimed to compare three different combinations, including propofol, ketamine, and ketofol, to determine an optimal protocol to be used during MRI scanning in the pediatric population. Our results imply that utilization of ketofol in children receiving sedation during MRI scanning provides a larger upper airway cross-sectional area at the level of the BOT, soft palate, and epiglottis without an increase in the risk of hemodynamic compromise and complication rate compared to those receiving propofol or ketamine separately. The total duration of the scanning procedure and recovery time were also significantly shorter in children receiving ketofol than that of propofol or ketamine.

Magnetic resonance imaging is commonly used in the pediatric patient population, and the comfort of the patient is an important issue for a successful scanning procedure. Even though all three protocols for sedation provided sufficient depth of anesthesia to achieve the scans, more is required to distinguish which anesthetic regimen was optimal.[11] Different changes have been observed regarding heart rate, blood pressures, upper airway dimensions, and res-

piratory rates. It is difficult to establish a causal relationship between the alterations in the upper airway size and other variables.

It has been reported that Cine MRI provides a sufficient method for imaging all levels of the upper airway simultaneously. By this method, various measurements may be performed with relative objectivity. For this purpose, a cine MRI should be implemented with anesthetic protocols that imitate natural sleep. The utility of cine MRI for the detection of upper airway obstruction can be popularized by the elimination of the technical challenges linked with the anesthetic administration, and other clinical challenges encountered in this high-risk pediatric population. The use of Cine MRI for predicting the severity of OSAS has been advocated in the relevant literature.[12]

Propofol is widely utilized for anesthesia and sedation of the children due to its extremely rapid onset and brief duration of action.[13] However, it decreases the cross-sectional area of the entire pharyngeal airway even in patients with normal upper airway morphology.[14] Moreover, hypotension presenting during induction seldom limits its common use for sedation in children. The potential reduction in blood pressure might be significant enough to result in clinical hypoperfusion, and occasionally lead to a temporary decrease in end-organ perfusion.[15]

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist and is also frequently used in induction and maintenance of general anesthesia and sedation in the pediatric population with the advantages of rapid onset, short duration of action, as well as procedural amnesia and analgesia. Periprocedural nausea and vomiting, hallucination, and long recovery time are the main drawbacks of ketamine use.[9]

In sedation of the pediatric population, the ideal approach should involve complete and precise evaluation of peri-procedural risks and the provision of upper airway management. This approach necessitates the capability to secure difficult airways in children presenting with various clinical entities. Despite the relatively recent use of ketamine and propofol in the practice of sedation in anesthesia, elimination of unwanted effects due to the individual use of these drugs popularized combination protocols. The medications preferred for sedation should have a quick onset of action, must be readily available at an affordable price and easy to administer. Rather than seeking a single medication with all these features, the combined use of ketamine and propofol may provide advantages to meet this demand and potentially improve sedation by reducing the toxicity of each drug alone.

Moreover, the analgesic, complementary and additive effects of these agents may be achieved by combined use. Combination regimens allow the anesthesiologist to reduce the drug doses and to decrease the frequency and severity of some of the side effects. Elimination of these side effects is especially important in children because they are more prone to be unstabilized after the administration of these anesthetic agents.

Ketofol, consisting of two pharmaceutically compatible drugs when mixed together in the same syringe, therefore, has rendered attention for use in pediatric sedation in recent years. Its favorable effects in adult subjects in terms of reducing the cardio-respiratory problems, psychomimetic complications, and nausea and vomiting have been demonstrated in a recent meta-analysis of 18 clinical trials.[16] Ketofol has also been shown to provide adequate sedation, analgesia, and rapid recovery with hemodynamic stability and minimal respiratory depression in children undergoing various kinds of surgery and diagnostic procedures.[17-19] Kip and colleagues have reported that the implementation of decreased ketamine doses in ketofol mixture was related to decreased side effect profile, high parent satisfaction with fast recovery in children undergoing dental treatment.[20] However, the utilization of ketofol in children undergoing MRI scanning and its impact on upper airway size and hemodynamic parameters during the procedure has not been investigated yet.

The present study is the first to demonstrate the beneficial effects of ketofol on upper airway size and recovery time when compared with the single use of propofol and ketamine in children undergoing MRI scanning. Our results showing the favorable hemodynamic parameters obtained with ketamine confirm

the extensive data derived from several procedures. With this background in mind, we suggest that the implementation of ketofol in the sedation of children undergoing MRI scanning will provide rapid recovery and better airway size with acceptable frequency of complications.

Main weaknesses of the present study that merit comment is retrospective design, data limited to the experience of a single-center, and small sample size. Our study population was comprised of children with a wide age range of children on includes a wide age range (1-12 years). Our series was comprised of a heterogeneous group of patients with a spectrum of clinical complexities and without age-matched controls. Further prospective, controlled trials on larger series are necessary to make more accurate interpretations.

CONCLUSION

In conclusion, ketofol, the combination of ketamine and propofol, provides an effective and safe anesthetic regimen for magnetic resonance imaging in the pediatric population. Our results show that ketofol-based sedation also provides a larger upper airway size without the development of any hemodynamic derangement. We suggest that utilization of ketofol should be considered in children receiving sedation for MRI scanning.

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülseren Yılmaz;* ***Design:*** *Osman Esen;* ***Control/Supervision:*** *Abdurrahim Derbent;* ***Data Collection and/or Processing:*** *Nevin Aydın;* ***Analysis and/or Interpretation:*** Kenan Varol; ***Literature Review:*** *Arda Kayhan, Ziya Salihoğlu;* ***Writing the Article:*** *Gülseren Yılmaz;* ***Critical Review:*** *Ziya Salihoğlu, Arda Kayhan;* ***References and Fundings:*** *Gülseren Yılmaz;* ***Materials:*** *Gülseren Yılmaz*.

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