A Comparison of Dexmedetomidine Versus Midazolam for Sedation and Hemodynamic Control During Femoral Embolectomy Performed Under Local Anesthesia

Lokal Anestezi Altında Femoral Embolektomi Sırasında Sedasyon ve Hemodinamik Kontrol için Uygulanan Deksmedetomidin ve Midazolamın Karşılaştırılması

Vedat YILDIRIM, MD,[a]
Suat DOĞANCI, MD,[b]
Artan JAHOLLARI, MD,[b]
E. Arzu KÖSE, MD,[c]
Ufuk DEMİRKILIÇ, MD,[b]
Ahmet ÇOŞAR, MD[a]

Department of Anesthesiology and Reanimation,
Cardiovascular Surgery,
Gulhane Military Academy of Medicine,
Clinic of Anesthesiology,

Yazışma Adresi/*Correspondence:*
Vedat YILDIRIM, MD,
Department of Anesthesiology and Reanimation,
Gulhane Military Academy of Medicine,
06018, Ankara,
TÜRKİYE/TURKEY
drvyildirim@yahoo.com

ABSTRACT Objective: Femoral artery (FA) embolectomy surgery is commonly performed under local anaesthesia with midazolam sedation. Dexmedetomidine is a highly selective α-2 agonist with sedative, analgesic, and anxiolytic effects and its use in FA embolectomy surgery has not been reported. This double-blind study compared the use of dexmedetomidine and midazolam in patients undergoing FA embolectomy. **Material and Methods:** Forty patients undergoing femoral embolectomy under local anaesthesia randomly received either i.v. dexmedetomidine (Group I) (n=20) 1 microg/kg over 10 min; followed by 0.1-0.6 μg/kg/h i.v. infusion, or midazolam (Group II) (n=20) 20 μg/kg i.v.; followed by 0.5 mg i.v. boluses as required. Sedation was titrated to a Ramsay sedation score of 2-4. Mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO2), readiness for recovery room discharge (time to Modified Post Anesthesia Discharge Scoring System (MPADSS) score of 9-10), and patients' pain scale (on NRS scaling system) were determined. **Results:** MAP and HR were lower in Group I compared with Group II. Group I patients had slightly lower postoperative supplemental fentanyl need when compared with patients in Group II. Group II patients had slightly higher respiratory rate, but this was not statistically different from group I. There was no difference for SpO2 between two groups. MPADSS score 9 and 10 were significantly higher in Group I. **Conclusion:** Compared with midazolam, dexmedetomidine appears to be suitable for sedation in patients undergoing femoral embolectomy surgery. While recovery room discharge was a little longer, there was a slightly better subjective patient satisfaction and it was accompanied by haemodynamic profile amelioration desirable in patients undergoing FA embolectomy who have more frequent coronary artery disease and are at greater risk for perioperative myocardial ischemia than the general population in group I.

Key Words: Sedation, midazolam, dexmedetomidine, femoral embolectomy

ÖZET Amaç: Femoral arter (FA) embolektomi cerrahisi yaygın olarak lokal anestezi altında midazolam ile sağlanan sedasyonla yapılır. Deksmedetomidin oldukça seçici bir α-2 agonisttir. Sedatif, analjezik ve anksiyolitik etkileri vardır. FA embolektomi cerrahisinde kullanımı henüz bildirilmemiştir. Bu çift-kör çalışmada FA embolektomisi uygulanan hastalarda deksmedetomidin ve midazolamın kullanılması karşılaştırılmıştır. **Gereç ve Yöntemler:** Lokal anestezi ile femoral embolektomi uygulanan 40 hasta iki gruba randomize edildi. Grup I'deki hastalara 10 dk'da 1 mikrogram/kg deksmedetomidine ve bunu takiben 0.1-0.6 μg /kg i.v. infüzyonla verildi. Grup II'deki hastalara ise 20 μg /kg dozunda midazolam verildi ve gerektiğinde i.v. 0.5 mg bolus uygulandı. Sedasyon Ramsay sedasyon skoru 2-4 olacak şekilde ayarlandı. Ortalama arter basıncı (MAP), kalp hızı (HR), solunum sayısı (RR), oksijen satürasyonu (SpO2), yoğun bakımdan çıkmaya hazır olma (Modified Post Anesthesia Discharge Scoring System)(MPADSS) skoru 9-10 olmak için geçen süre ve hasta ağrı skoru (NRS skalası üzerinden) değerlendirilerek kayıt edildi. **Bulgular:** Grup II ile karşılaştırıldığında Grup I'de MAP ve HR daha düşüktü. Grup I'deki hastalarda postoperatif destek fentanil ihtiyacı Grup II'deki hastalar ile karşılaştırıldığında hafifçe daha azdı. Her ne kadar istatistiksel olarak anlamlı olmasa da, Grup II'deki hastalarda solunum sayısı hafifçe daha yüksekti. Gruplar arasında oksijen satürasyonu yönünden fark yoktu. MPADSS skoru 9 ve 10 Grup I'de anlamlı olarak daha yüksekti. **Sonuç:** Midazolam ile karşılaştırıldığında deksmedetomidine femoral embolektomi cerrahisi uygulanan hastalarda sedasyon için uygun gibi gözükmektedir. Her ne kadar yoğun bakımdan çıkmak için hazır olma süresi biraz daha uzun olsa da, grup I'de hasta memnuniyeti biraz daha iyiydi. Bunun yanında daha sıklıkla koroner arter hastalığı bulunan ve perioperatif miyokardiyal iskemi gelişme riski daha yüksek olan femoral embolektomi uygulanan hastalarda deksmedetomidine ile daha iyi hemodinamik profil sağlanabilir.

Anahtar Kelimeler: Sedasyon, midazolam, deksmedetomidin, femoral embolektomi

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Acute lower limb ischemia (ALI) remains the commonest vascular surgical emergency. Thrombo-embolism, usually secondary to atrial fibrillation, accounts for around a third of cases. Although, from a technical view-point, femoral embolectomy appears to be a straight-forward procedure, it must be remembered that thromboembolic ALI is associated with an in-hospital mortality of around 20-25%. Accurate diagnosis, patient selection, preoperative preparation, postoperative care as well as attention to detail in the performance of the embolectomy are essential if morbidity and mortality are to be minimized; 'failed' embolectomy is associated with a poor outcome.[1]

Patients suffering from acute peripheral artery occlusion generally have an atherosclerotic profile or have cardiac co morbidities. Maintaining a stabile haemodynamic state is essential in preventing peri or postoperative myocardial ischemia and other complications. Several studies have shown that haemodynamic stabilization by the application of α_2-adrenoceptor agonists in the perioperative period leads to a reduction in perioperative myocardial ischemia episodes.[2]

Femoral embolectomy is a procedure frequently performed under local anesthesia with monitored anesthesia care and sedation. Several drugs have been used for sedation during this procedure including propofol, benzodiazepines, and opioids.[3-5] However, propofol may cause oversedation and disorientation,[3] benzodiazepines may result in confusion, particularly, when administered to elderly patients,[4] and opioids are associated with increased risk of respiratory depression and oxygen desaturation.[5]

Dexmedetomidine is a potent, highly selective α_2-adrenoceptor agonist, and represents the most recently developed and released agent in this pharmacological class. The well-documented beneficial effects of α_2-adrenoceptor agonists include anxiolysis, analgesia, sedation and sympatholysis, thus rendering these compounds especially suitable for anesthesia at perioperative and postoperative period.[6]

Midazolam is commonly used as and intravenous sedative agent for surgical procedures. It has quick onset and rapid recovery, but the drug and its metabolite have a relatively long half-life. After repeated administration, there may be prolongation of sedation and hangover effects, such as excessive sleepiness and psychomotor impairment.[7] Moreover, it depresses the ventilatory response to carbon dioxide and results in respiratory depression.[8] Some patients may also develop disinhibition and disorientation and become unable to comply with treatment.[9]

We therefore decided to investigate, in a prospective double-blind randomized controlled trial, whether dexmedetomidine could provide effective sedation as well as greater hemodynamic stability than a conventional sedation regimen comprised of midazolam.

MATERIAL AND METHODS

After obtaining written, informed consent from all patients and approval from the ethics committee, 40 patients, aged 42-81 years, scheduled to undergo Femoral embolectomy surgery were included in this study.

They were excluded if they had history of chronic use of sedatives, narcotics, or both, history of alcohol or drug abuse, serum creatinine>200 μmol/litre, advanced liver disease-liver enzymes twice the normal range or higher- or allergy to any of the study medications. Using a computer-generated randomization schedule, patients were randomized to receive either dexmedetomidine (Group I) (n=20) or midazolam (Group II) (n=20) for sedation during surgery.

Patients arrived in the operating room unpremedicated. In all patients, heart rate, blood pressure and pulse oximetry were measured non-invasively. Oxygen was administered at 2 litre min. Peripheral venous cannulation was performed on the dorsum of the right hand.

The anesthetist was blinded to the patient's group assignment, and the study data were recorded by a blinded observer. Drugs were prepared by another anesthetist who is unblind to procedure

(EAK) and were delivered to the anaesthetist in three maximally filled-up syringes. The largest syringe (size 50 ml) was labelled 'infusion drug', a 5 ml syringe was labelled 'repeat boluses' and a 3 ml syringe was labelled 'initial bolus'. Group I patients had dexmedetomidine 4 μg/ml in the 50 ml syringe and saline in the other two syringes; whereas Group II patients had saline in the 50 ml syringe, midazolam 1 mg/ml in the 5 ml syringe, and midazolam 20 μg/kg (based on patient's body weight) premixed with saline to a total volume of 3 ml in the 3 ml syringe.

In all patients level of sedation throughout the procedure was assessed using the Ramsay Sedation Score (RSS) (Table 1).[10] The aim was to maintain the patient in the range of 2-4.

GROUP I

Initial loading dose of dexmedetomidine (1 μg/kg) over 10 min and normal saline 3 ml i.v. bolus (from the 'initial bolus' syringe) followed by infusion at 0.2-0.6 μg/kg/h from the 50-mL "Infusion" syringe and titrated every 10 min, in steps of 0.1 μg/kg/h, to a Ramsay sedation scale of 2-4. Furthermore, with each increment in the infusion rate of dexmedetomidine, normal saline 0.5 ml i.v. bolus was administered concomitantly (from the 'repeat boluses' syringe) to maintain blinding.

GROUP II

Patients received normal saline 0.25 ml kg i.v. over 10 min using the infusion pump and the 50 ml syringe labeled 'infusion drug', along with midazolam 20 μg/kg i.v. bolus (from the 'initial bolus' syringe). This was followed by normal saline infusion starting at 0.1 ml/kg/h and titrated every 10 min, in steps of 0.025 ml/kg/h, to a Ramsay sedation scale of 2-4. In addition, with each increment in the infusion rate, midazolam 0.5 mg i.v. (from the 'repeat boluses' syringe) was administered. The infusion pump was stopped at the end of the procedure in both groups.

After initiation of sedation, the operative site was anesthetized with local anesthesia using prilocain HCL 20 mg/ml. Local anesthesia was performed by the surgeon and was in the range of 30-40 ml.

Heart rate (HR), blood pressure (taken with a noninvasive method), SpO_2 (by pulse oxymetry), and respiratory rate (RR) were measured in every 60 seconds during the first 10 minutes, every 2 minutes during the second 10 minutes, every 5 minutes from 20 to 60 minutes, and every 10 minutes until the patient was fully recovered. All measurements were noted by using automated monitors and intensive care unit nurse staff. The nurses were blinded to the patients. Complications such as apnea, desaturation, cough, abnormal movements, and postoperative nausea and vomiting (PONV) were recorded. Apnea was defined as the absence of spontaneous respirations for at least 20 seconds; desaturation was defined as SpO_2 below 90%.

The primary outcome variable was the number of pharmacological interventions required to treat deviations of systolic blood pressure (BP) or HR outside predetermined limits; recovery time from anesthesia (evaluated by MPADSS scale). Baseline BP and HR were taken from the patients' attendance at a preoperative room before going to surgery. Systolic BP was to be maintained within 30% of baseline as well as within the absolute limits of 100-180 mmHg. HR was also maintained within 30% of baseline and within the absolute limits of 45-100 bpm. Hypotension was treated with a vasopressor (ephedrine) or an IV fluid bolus, bradycardia with a chronotrope (atropine) or ephedrine, hypertension with an IV infusion of glyceryl trinitrate, and tachycardia with a β-adrenergic blocker.

TABLE 1: Ramsay Assessment Scale for the level of sedation.

Description	Score
Patient paralyzed, unable to assess level of sedation	0
Patient anxious, agitated, or restless	I
Patient cooperative, oriented, and tranquil	II
Patient sedated but responds to commands	III
Patient asleep but responds to glabellar tap	IV
Patient asleep but responds to nail bed pressure (no response to glabellar tap)	V
Patient asleep, no response to nail bed pressure	VI

All of these drugs were administered in doses consistent with clinical practice. The number of interventions and doses of individual drugs were recorded.

In the recovery room, Modified Post Anesthesia Discharge Scoring System (MPADSS) (Table 2).[11] was determined every 5 min until discharge and the requirement for postoperative analgesia was documented. Patients were deemed ready for discharge when they had achieved a MPADSS score of 10. The time was measured to the moment, in which the MPADS score reached 10 points according to patient responses. The results were compared between the study groups.

All adverse events including, but not limited to, bradycardia (HR <60 beats min^{-1}), hypotension (MAP <60 mm Hg sustained for >10 min), respiratory depression (ventilatory frequency 10 bpm), oxygen desaturation (SpO_2<90%) or unplanned hospital admission were recorded.

The quality of analgesia was assessed by the patients on a scale of 0 to 10 (11 points) named Numerical Pain Rating Scale (NRS). The patients were asked to indicate the intensity of the pain experienced on the scale with 0 being "no pain at all" and 10 "the worst pain imaginable".

Administration of any medication apart from the study protocol and occurrences of complications and side effects (strong vertigo, nausea, vomiting) were recorded. In case of serious adverse events, the study protocol provided for hospital admission to an observation ward for minimum of 12 h. Patients were also asked about their willingness to undergo a repeat procedure with the same sedation regimen in the future if required.

STATISTICAL ANALYSIS

Results were expressed as numbers of occurrences, percentages, and mean ± SD for continuous variables. In some cases, the data were presented as percent changes for clarity. Categorical data were analyzed using the chi-square test with a Yates correction or Fisher exact test, where appropriate. NRS scores were not normally distributed and were compared between groups using a nonparametric Kruskal-Wallis test. The differences in continuous parameters such as patient characteristics, preoperative data, time intervals, and amounts of supplemental fentanyl were analyzed using one-way analysis of variance. Repeated-measures analysis of variance was used to test for the difference between groups in HR, MAP, respiratory rate, and SpO_2 over time. Correction with *post hoc* tests (Bonferroni method) was used because repeated

TABLE 2: Modified post anesthetic discharge scoring system.

Category	Description	Score
Vital signs	Within 20% of preoperative value	2
	Within 20%-40% of preoperative value	1
	Within 40% of preoperative value	0
Ambulation	Steady gait/no dizziness	2
	With assistance	1
	None/dizziness	0
Nausea/vomiting	Minimal	2
	Moderate	1
	Severe	0
Pain	Minimal	2
	Moderate	1
	Severe	0
Surgical bleeding	Minimal	2
	Moderate	1
	Severe	0

measurements of a single variable were tested over time. A *P* value of less than 0.05 was considered significant. Statistical analyses were performed using Statistica for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics and anesthesia time were similar between group I and group II (p>0.05, Table 3). There were no differences in baseline measurements of HR and MAP between groups, patients in Group I had lower HR and MAP over time compared with those in Group II (P<0.05) (Figure 1a, 1b). Respiratory rates and hemoglobin oxygen saturation were showed in Fig 1c and 1d. Respiratory rates were similar between groups, but oxygen saturation was lower in Group II during drug infusion (p = 0.003) and lower in during surgery (p = 0.03). Oxygen desaturation (oxygen saturation lower than 90%) occurred in three patients (15%) who received group II (p = 0.488). Oxygen saturations rapidly returned to normal upon treatment. A jaw thrust maneuver had to be applied in 6 of the cases (30 %) in group II. This was not required in group I. The lowest oxygen saturation observed in any patient was not lower than 90% during the procedure**.** Intubation was not necessary in any case. Neither laryngospasm nor bronchospasm were observed in any patient and there were no significant differences in the incidence of other complications.

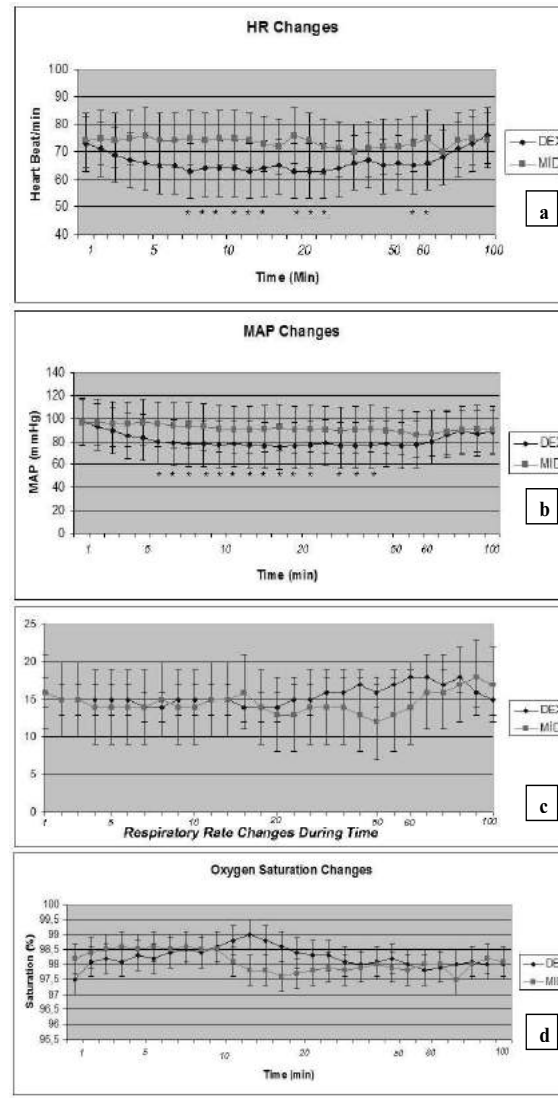

FIGURE 1: Changes in respiratory rates (a), mean arterial pressure (MAP) (b), oxygen saturation (c), and heart rate (HR) (d) over time. (DEX: Dexmedetomidine, MID: Midazolam).

TABLE 3: Patient characteristics.

	Group I (n=20)	Group I (n=20)	P value
Age (yr)	63.1±7.1	62.7±6.9	NS
Weight (kg)	70.1±10.6	69.4±11.0	NS
Gender (male/female)	15/5	16/4	NS
ASA I/II/III	1/14/5	1/15/4	NS
Preexisting disease			
Hypertension (n)	12	13	NS
Ischemic hearth disease (n)	5	5	NS
Diabetes mellitus (n)	10	3	NS
Congestive cardiac failure (n)	2	3	NS
Medications			
Beta-adrenergic blockers	10	9	NS
Calcium channel blockers	6	5	NS
Angiotensin-converting enzyme	8	9	NS
Anesthesia time (min)	49.1±19.2	51.4±15.2	NS

The NRS score was not different among the study groups (*P*= 0.949; Figure 2). Vertigo and nausea, followed by vomiting treated with ondansetron, occurred in 1 case in group II. No vertigo or nausea was observed in group I. The average duration of femoral embeloctomy in group I (49.1±19.2 min) was approximately same in group II (51.4±15.2 min). In group I, the time required to reach home discharge readiness (10 points on the MPADSS scale) was significantly longer (65±49

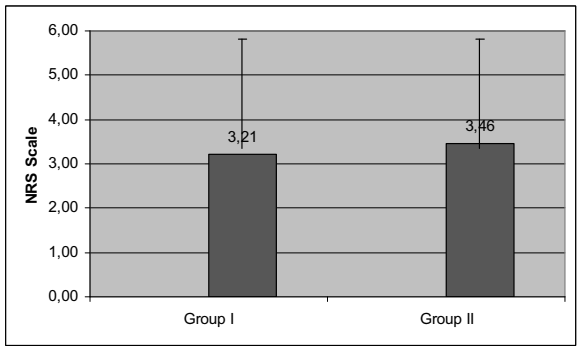

FIGURE 2: Comparison of the intensity of pain, according to the Numerical Pain Rating Scale (NRS) in the study groups. Data are presented as mean and SD; vertical lines represent SDs. Group I = dexmedetomidine group; and group II = midazolam group. P > 0.05.

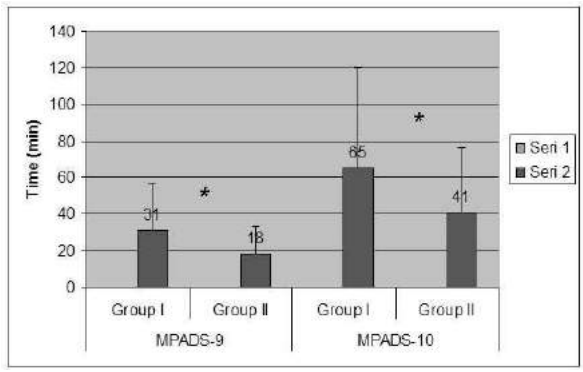

FIGURE 3: Time intervals from the end of femoral embolectomy until scores of 9 or 10 were reached in the Modified Post Anesthesia Discharge Scoring System (MPADSS). Data are presented as mean and SD; vertical lines represent SDs. MPADSS-9 = end of procedure until 9 points on MPADSS; MPADSS-10 = end of procedure until 10 points in MPADSS. * P < 0.01.

min) compared with the group II (41±22 min). Group I patients were delayed in achieving MPADSS scores of both 9 and 10 (*i.e.*, ready for discharge to home) compared with two groups (Figure 3).

No major adverse effects were observed in this study including unplanned hospital admission or conversion to general anesthesia. Only four patients in Group II requested analgesia in the recovery room and all of them had received a single dose of fentanyl 25 mg i.v. All the patients were haemodinamically stable in the recovery room. Both groups had a similar difference in hemodynamic parameters before and at two hours after surgery. NRS pain scores during local anesthetic infiltration, in the ward and at two days postoperatively were similar.

DISCUSSION

This study shows that dexmedetomidin, used as an infusion during femoral embolectomy performed under regional anesthesia, is associated with less intraoperative and postoperative hypertension and tachycardia while maintaining similar degrees of sedation when compared with a conventional sedative technique. Both techniques provided similar patient satisfactory levels.

Dexmedetomidine is a potent, highly selective α_2-adrenoceptor agonist, and represents the most recently developed and released agent in this pharmacological class. The well-documented beneficial effects of α_2-adrenoceptor agonists include anxiolysis, analgesia, sedation and sympatholysis, thus rendering these compounds especially suitable for anesthesia and the perioperative period. Dexmedetomidine, like other α_2-adrenoceptor agonists, displays a biphasic, dose-dependent blood pressure response. High doses produce a hypertensive response caused by the activation of α_{2B}-adrenoceptors on vascular smooth muscle. This prohibits the rapid intravenous injection of dexmedetomidine. The dominant action of α_2-adrenoceptor agonists with low and clinically recommended concentrations is hypotension caused by a centrally mediated sympatholysis and by the inhibition of neurotransmission in sympathetic nerves.[12-14] Dexmedetomidine possesses a dose-dependent bradycardic effect, mediated primarily by the decrease in sympathetic tone and partly by baroreceptor reflex and enhanced vagal activity.[12,13,15,16]

We were unable to detect a significant difference in the overall rate of hemodynamic interventions when comparing dexmedetomidine to midazolam; however differences in the indications for these interventions were significant. In particular, patients in group I were less likely to require treatment for hypertension and/or tachycardia. This presumably reflects the action of dexmedetomidine on central α_2 adrenoceptors resulting in a reduction of sympathetic tone and lower catecholamine levels.[17,18]

Our study demonstrates that dexmedetomidine can provide comparable sedation when compared

to midazolam for femoral embolectomy under local anaesthesia. A lower heart rate and blood pressure can be achieved by using dexmedetomidine.

Scheinin H et al.[19] suggested that lower HR and MAP observed in dexmedetomidin could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine. Similar haemodynamic changes have been reported by Arain and Ebert[9] who compared dexmedetomidine with propofol for sedation during surgery under regional anaesthesia.

In a study made by J. A. Alhashemi[20] comparing dexmedetomidine and midazolam in cataract surgery higher ventilation frequency and lower SpO_2 values were found in midazolam group. We have found similar values and we think that this could not have been caused by patients' discomfort during surgery as none of them required supplemental analgesia intraoperatively, and satisfaction scores with analgesia were nearly identical in both study groups. It is possible, however, that midazolam had resulted in decreased patients' tidal volume, and the observed increase in ventilatory frequency. This was a compensatory response to maintain minute ventilation. In support of this hypothesis is the observed trend towards lower SpO_2 in Group II, which would suggest that breathing was likely shallow with consequent atelectasis and ventilation–perfusion mismatch. In contrast, it is unlikely that the lower SpO_2 in Group II was responsible for the increase in ventilatory frequency in this group as none of the patients had an $SpO_2$90%. But this was not statistically different from group I ($p>0.05$).

In a study by Jalowiecki P et al.,[21] the times to discharge readiness were significantly longer when dexmedetomidine was used, in some patients requiring several hours. This observation tried to explain by the pharmacokinetic properties of dexmedetomidine, which has an elimination half time of approximately 2 h. The most frequent reasons for delay in reaching the target MPADSS score in this group was variations in arterial pressure and HR exceeding 20-40% of baseline, prolonged sleepiness, weakness, and nausea. The increased frequency of the adverse events in patients receiving dexmedetomidine partially explained by the use of supplemental opiate because fentanyl was administered in cases of inadequate analgesia in all three study groups. In our study, MPADSS score was also similarly lower in Group I patients, although we did not use opiates in our patients. Patients in group I reached the score of 9-10 for longer duration time from group II, this delay was also prominently due to prolonged sleepiness.

Jalowiecki P et al.[21] reported similar NRS score (<4) in all study groups. In this study in 47% of cases, adequate pain relief in patients receiving dexmedetomidine could be achieved only with supplemental fentanyl. On the other hand McCutcheon CA et al.[22] reported that when dexmedetomidine used for sedation during CEA under regional anesthesia, provided reliable and titratable sedation. It produced mild analgesic effects that decreased analgesic requirements postoperatively. In our study NSR score were similar in both groups. But the need for supplemental fentanyl during the postoperative period was higher in group II (20% of the patients in group II needed supplemental fentanyl). Although this finding was conflicting with Jalowiecki P, it was in accordance with McCutheon CA et. al's results.

In conclusion, we found that dexmedetomidine, when used for sedation during femoral embolectomy under regional anesthesia, provided reliable and titratable sedation. It produced mild analgesic effects that decreased analgesic requirements postoperatively and had a hemodynamic profile characterized by moderate reductions of HR and BP that persisted into the postoperative period. These characteristics are desirable in patients undergoing femoral embolectomy who have more frequent coronary artery disease and are at greater risk for perioperative myocardial ischemia than the general population. However the potential for hypotension and bradycardia when using dexmedetomidine in these patients highlights the need for vigilant hemodynamic monitoring throughout the perioperative period. Another advantage of hypotension during surgery also may be lower hemorrhage during surgery and lower postoperative hematoma rates. Some larger studies are needed to confirm such advantages.

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