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Comparison of Midazolam and Dexmedetomidine when Combined with Fentanyl for Percutaneous Transluminal Angioplasty in Patients with Peripheral Artery Disease

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Abstract:

Background and Aim: Percutaneous transluminal angioplasty (PTA) is increasingly being performed for management of peripheral artery disease. Patients undergoing PTA experience significant intraoperative and post operative pain. This study compared the anaesthetic efficacy of dexmedetomidine and midazolam, when combined with fentanyl in patients undergoing PTA.

Material and Methods: Hundred patients posted for lower limb PTA were randomized into two groups receiving either intermittent midazolam boluses (0.03–0.05 mg/kg) (M group) or dexmedetomidine 0.3–0.6 µg/kg/h after a loading dose of 1.0 µg/kg for 10 min (D group), both with fentanyl. The primary outcome was the patients' procedural satisfaction. Secondary outcomes included postprocedural VAS scores and adverse effects.

Results: The satisfaction level of patients was significantly better in the D group compared with the M group (4.0 [3.0, 5.0] versus 4.0 [2.0, 5.0] p = 0.021). The number of patients having a postprocedural VAS score of at least 4 was significantly higher in the M group compared with the D group (10 [20%] versus 2 [4%], p = 0.013). Adverse events and hemodynamic parameters did not defer between the two groups,

Conclusion: The use of dexmedetomidine in along with fentanyl may be a safer option that provides excellent patient satisfaction while decreasing postprocedural pain.

Key Words: Dexmedetomidine, Fentanyl, Midazolam, Percutaneous Transluminal Angioplasty

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Introduction

The prevalence of peripheral artery disease (PAD) and its related morbidities are escalating in our present population[1]. Percutaneous transluminal angioplasty (PTA) is being increasingly performed for management of PAD. Therefore, there is need for proper anaesthetic management for these patients[2]. Presently, many cardiovascular procedures that require monitored anaesthetic care (MAC) are performed using a fentanyl-based anaesthesia for its superb analgesic effects, cardiovascular stability and pharmacokinetic advantage of rapid elimination [3,4]. However, fentanyl may cause respiratory depression and has no sedative effects [5,6]. Contrary to that, sedatives such as midazolam and propofol have no analgesia. Their use with opioids increases the risk of respiratory depression which may require advanced airway support [7].

Anaesthetic management for PTA can be complicated by certain factors. Firstly, patients with PAD share same risk factors as patients with cardiovascular diseases and show 2- to 6-times greater risk of cardiac events [1,8]. Second, patients with PAD have variable spectrum of intensity and character of pain [1] possibly owing to endovascular ballooning which causes ischemic pain as well. Patients may experience pain even after 24 hours of revascularization procedure which may be due to due to oxidative stress and inflammatory response [9]. Therefore, anaesthetic regimen that maintains a balance between patients' safety and satisfaction needs to be made.

Dexmedetomidine is a highly selective alpha 2 agonist that has good properties of both sedation and analgesia whilst not causing respiratory depression [10]. Previous studies proved its favourable effects on respiration and interventionists' satisfaction in catheter ablation for atrial fibrillation [4]. In reference to PTA, dexmedetomidine may also be beneficial for post reperfusion pain as it has been shown to exert anti-oxidant and anti-inflammatory effects in animal models of ischemia-reperfusion injury [11,12]. Therefore, we hypothesized that the addition of dexmedetomidine to a fentanyl-based monitored anaesthesia care regimen for angioplasty would improve patients' satisfaction without respiratory depression and extends postprocedural analgesic effects.

The primary aim of this randomized, controlled study was to compare the anaesthetic efficacy of dexmedetomidine and midazolam in PTA by comparing the patients' satisfaction. Secondary endpoints were interventionists' satisfaction, pain intensity and postprocedural analgesic requirements up to 24 h after the procedure, and the occurrence of drug-related adverse events.

Material and Methods

This study was randomised double blind trial. After taking informed consent from each patient, 100 patients with ASA status I to III, aged 30-70 years, who were posted for PTA for lower limb lesions under monitored anaesthesia care between October 2021 and March 2023 were enrolled. We excluded patients with psychiatric disorder, cognitive impaired neurological diseases, myocardial infarction and/or stroke, liver diseases, or congestive heart failure. Patients were randomly and evenly allocated to either midazolam plus fentanyl (Group M, n = 50) group or dexmedetomidine plus fentanyl (Group D, n = 50) group by a computerized randomization table. Blinding of the group designation was maintained to the patients and the attending anaesthesiologist and interventionists, while the study drugs were prepared by a trained anaesthetist who was not involved in patient care or assessment.

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In the M group, 0.03–0.05 mg/kg of midazolam was given as intermittent boluses, while the patients in the D group received same amount of 0.9% saline boluses. In the D group, 1.0 μg/kg of dexmedetomidine loading dose was given in 100ml 0.9%NS over 10 minutes and then maintenance was done until the end of the procedure at infusion rates of 0.3–0.6 μg/kg/h while the M group received same infusions of 0.9% saline. Dose was adjusted to target the Ramsay sedation score of 2 to 3[13].

Intraoperatively, MAC was initiated using either M or D regimen. Local anaesthesia with 2 % lidocaine to the ipsilateral and/or contralateral inguinal area were also given before arterial access. In all patients, continuous infusion of fentanyl at 1.2 μg/kg/h using an infusion pump was started along with the bolus dose of midazolam or dexmedetomidine. The fentanyl infusion rate was increased by 0.6 μg/kg/h and up to 7.2 μg/kg/h to maintain the pain score ≤3. Fentanyl infusion rate was decreased by 0.6 μg/kg/h until reaching 0.6 μg/kg/h when the pain score was between 0 and 1.

In the postprocedural period, patients were given acetaminophen and tramadol as rescue analgesics upon their request or when the pain score exceeded 4. The choice of the rescue analgesic was done at the discretion of the attending physician at the ward. To compare the doses, substitution was made with equipotent doses of fentanyl.

All demographic factors, intraprocedural pain, hypotension, bradycardia, any other complications were recorded. Post procedure patients were asked to rate their satisfaction score about their administered anaesthesia using a 5-point numerical rating scale (1 = extremely dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, and 5 = extremely satisfied) before being transferred. They were also asked for the overall VAS scores during the first 24 hours after the procedure. Patients were also asked for the frequency of having a pain score ≥3 during the study period. The number of patients requiring rescue analgesics, and the total amount of analgesics administered to the patients in fentanyl equivalent dose was recorded. After the end of procedure, the interventionists were asked to choose their satisfaction score for whom the same 5-point numeric rating scale was used.

Sample size calculation was calculated based on the patients' satisfaction score. In a previous study, the level of satisfaction by M regimen in catheter ablation for atrial fibrillation was 2.9 ± 0.7 [4]. If the use of dexmedetomidine instead of midazolam can enhance the satisfaction level by 0.5 or more, the estimated number of patients in each group was 41 ($\alpha = 0.05$ and power = 0.9). Accounting for any dropouts we decided to enrol 50 patients in each group.

Intergroup comparisons of satisfaction and pain scores were done by Mann-Whitney U test. Continuous variables were assessed for their distribution (Shapiro-Wilk test). Intergroup comparison of other variables that showed normal distribution were tested using the independent t-test (mean ± standard deviation [SD]). Skewed data were tested using Mann-Whitney U test (median [interquartile range]). Intergroup comparisons of categorical variables were tested using Chi-square test (n [%]). For pain scores that were assessed at 3 time points, post hoc Bonferroni correction was applied. Thus, the p values for the pain scores were considered statistically significant when <0.017. Otherwise, $p < 0.05$ was considered statistically significant.

Results

A total of 104 patients were screened, and 100 among them were enrolled and evenly randomized into either the M or D group (Figure 1).

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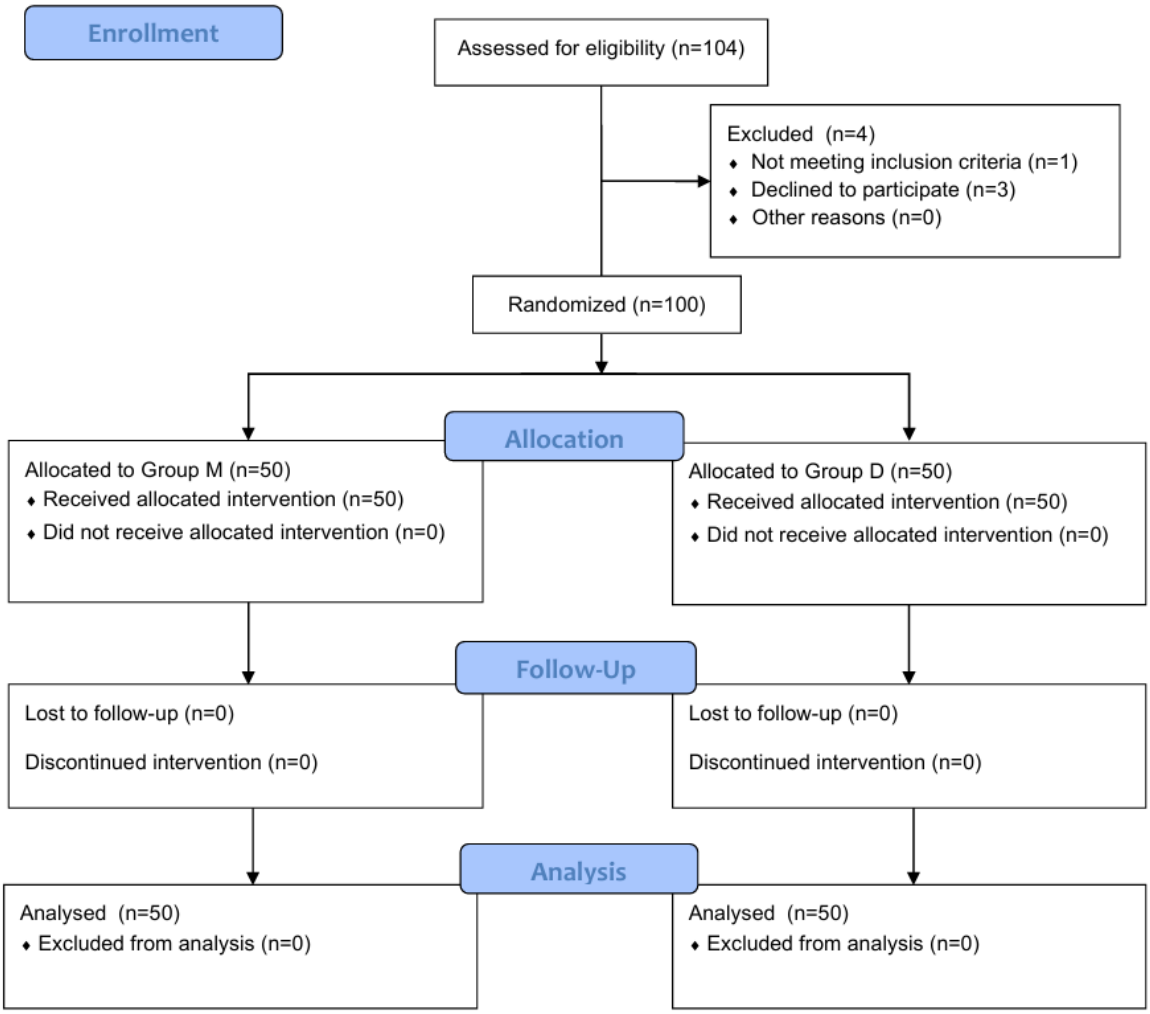

Figure 1. Research flow chart

Patients' characteristics and procedural data are displayed in Table 1. Patients' satisfaction (5-point numeric rating scale, 5 = extremely satisfied), which was the primary endpoint, was significantly greater in the D group compared with the M group (4.0 [2.0,5.0] versus 4.0 [2.0,5.0] p = 0.021) (Table 2). The satisfaction of the interventionists did not differ between the groups (Table 2). When analysing patients with considerable pain at rest (Rutherford category ≥4 having at least ischemic pain at rest), the patients' satisfaction score was more evidently in favour of the D group than the M group (4.0 [4.0,5.0] versus 3.5 [3.0,4.0], p = 0.046).

Table 1. Patients' Characteristics and procedural data.

Variables	M Group (n=50)	D Group (n=50)
Age (Years)	64.7 ± 12.5	64.1 ± 11.5
Sex (M/F)	44/6	47/3
Hypertension, *n* (%)	36 (72)	30 (60)
Diabetes Mellitus, *n* (%)	21 (44)	23 (46)
Coronary artery disease, *n* (%)	19 (38)	14 (28)

Chronic kidney disease, *n* (%)	1 (2)	2 (4)
Cerebrovascular accident, *n* (%)	3 (6)	5 (10)
Current smoker, *n* (%)	38 (76)	33 (66)
Procedure time (min)	59.7 ± 37.8	53.7 ± 31.4
Rutherford category		
1	1 (2)	2 (4)
2	8 (16)	5 (10)
3	19 (38)	21 (42)
4	15 (30)	13 (26)
5	5 (10)	7 (14)
6	2 (4)	2 (4)
Intraoperative medication		
fentanyl (μg/kg/h)	0.72 [0.50, 1.31]	0.72 [0.49, 1.06]
Midazolam (μg/kg/h)	20.51 [13.79, 44.44]	0 [0, 0]
Dexmedetomidine (μg/kg/h)	0 [0, 0]	51.00 [37.87, 74.40]

Data are displayed in mean ± SD, or n (%).

Table 2. Primary and secondary endpoints.

Variables	Group M	Group D	P-Value
Patients' satisfaction	3 [2,5]	4 [4,5]	0.021*
Interventionists' satisfaction	4 [4,4.5]	4 [3.5,4]	0.860
Baseline	2 [1,3]	2 [2,4]	0.734
Procedural	3 [0,4]	0.5 [0,4]	0.192
Post procedural 24 Hrs	0 [0,3]	0 [0,1]	0.213
Pain score >3	10 (20)	2 (4)	0.013*
Rescue analgesic	13 (26)	13 (26)	1.000
Rescue analgesic dose	10.0 [5.5,18.2]	6.6 [5.0,10.0]	0.062
Bradycardia	0	0	1.000
Hypotension	0	5 (10)	0.021*
Hypoxia	1 (2)	0	0.310
Nausea	0	1 (2)	0.310

Data are displayed in mean SD, n (%), or median (interquartile range). Satisfaction score was assessed using a 5-point numerical scale (1 = extremely dissatisfied~5 = extremely satisfied). * = $p < 0.05$. Pain score was assessed using an 11-point numeric scale (0 = no pain~10 = worst imaginable pain). Rescue analgesic dose was calculated as morphine equivalent dose. * = $p < 0.05$.

Hemodynamic data including heart rate and mean arterial pressure, and SaO2 were all within clinically acceptable ranges and showed no intergroup differences throughout the procedure. In terms of drug-related adverse events, inciwereces of bradycardia and hypoxia were not different between the groups, while the number of patients with 1 or more hypotensive episodes

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was higher in the D group compared with the M group, which could all be managed by a single bolus of intravenous ephedrine administration (Table 2).

Pain scores and the frequency of rescue analgesic requirement up to 24 h after the procedure were similar between the groups. However, the number of patients having a pain score of at least 3 was significantly greater in the M group compared with the D group (10 [20%] versus 2 [4%], p = 0.013), while the total amount of administered rescue analgesics in morphine equivalent dose showed a trend towards being lower in the D group compared with the M group (6.6 [5.0, 10.0] mg versus 10.0 mg [5.5, 18.2] mg, p = 0.062) (Table 2).

Discussion

Anaesthetic care for PTA can be challenging as patients with PAD comprise a high-risk group for cardiovascular events [14,15]. Thus, emphasis should be given to prevent anxiety or pain responses that cause maladaptive sympathetic activation during PTA. Also, successful PTA requires immobilization while confronting the fact that the patients already exhibit a broad spectrum of pain in addition to the ischemic pain elicited by intermittent ballooning.

For MAC during cardiovascular procedures, continuous infusion of fentanyl has become the mainstay of anaesthesia with the intermittent use of sedatives as necessary. Opioids have their advantages in that they are potent analgesics able to cover diverse pain characters and they lack direct myocardial depressant effects except for their central vagotonic influence [16]. However, in patients with rigorous pain, increasing the dose of remifentanil may not be feasible as opioids cause respiratory depression, which could be troublesome in a supine position with an increased risk of airway-compromise [5]. On the other hand, increasing the dose of sedatives may not suffice as the commonly used sedatives lack analgesic effects, and possibly also hyperalgesia lowering the pain thresholds [17], on top of increasing the risk of respiratory depression. Thus, finding an anesthetic regimen that provides adequate sedation without suppressing respiration would be of high priority for PTA.

Dexmedetomidine is a potent and selective alpha 2 agonist exerting sedative and analgesic effects at the same time without compromising respiration. Accordingly, emerging evidence supports its beneficial influence in critical care and MAC involving conscious sedation for cardiovascular procedures [4], while its anesthetic efficacy in PTA has never been validated heretofore. Moreover, nociceptive pain with PAD involves intermittent episodes of ischemia-reperfusion and its chronic manifestation has been shown to result in complex neuropathic pain as well [18]. Importantly, even successful PTA has been shown to elicit significant postprocedural pain related to reperfusion and oxidative stress [9,19]. Experimentally, dexmedetomidine has been shown to be effective in neuropathic pain through the inhibition of IL-6 and TNF-a [20]. Also, dexmedetomidine has been shown to attenuate oxidative and inflammatory stress responses related to ischemia-reperfusion [11,12]. Moreover, the EEG patterns observed during dexmedetomidine infusion more closely resembles those of the natural sleep as opposed to other anaesthetics [21], which may be favourable in terms of the sleep quality. Thus, we hypothesized that the use of dexmedetomidine in PTA would not only improve patients' satisfaction during the procedure, but also exert beneficial influence in postprocedural pain. As our results indicate, patients receiving dexmedetomidine were more satisfied with their anaesthetic care than those receiving midazolam with none of the patients in the D group reporting a satisfaction score of less than 3 (from a 5-point numeric scale with 5 being extremely satisfied) confirming our primary hypothesis. This beneficial effect of

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dexmedetomidine was even more evident in patients with considerable resting pain (Rutherford category ≥4). In terms of its efficacy on pain scores, we could only observe trends towards lower procedural and postprocedural pain scores in the D group compared with the M group. Interestingly, there were a significantly lower number of patients in the D group who experienced a significant postprocedural pain (pain scores of ≥3) than the M group, despite receiving a lower amount of rescue analgesics. Thus, per our hypothesis, the experimentally proven anti-inflammatory property of dexmedetomidine attenuating oxidative stress may have been responsible for the reduced incidence of intense pain after reperfusion in the current study. Also, concerns have been raised regarding a potential hyperalgesia phenomenon after discontinuation of remifentanil infusion that is not clearly understood [22]. Dexmedetomidine may also attenuate the hyperalgesia response after the discontinuation of remifentanil infusion by modulating spinal cord N-methyl-D-aspartate receptor activation via suppression of NR2B subunit phosphorylation [23], which may have contributed to the attenuated postprocedural pain.

In terms of drug-related adverse events, use of dexmedetomidine was associated with more frequent episodes of hypotension, which could all be rapidly restored by a single ephedrine bolus. This result agrees with our previous report involving patients undergoing catheter ablation of atrial fibrillation [4]. By being a sympatholytic, dexmedetomidine's potential to cause hypotension and bradycardia has been well acknowledged. Yet, its biphasic hemodynamic response usually shows an initial increase by mean arterial pressure with subsequent bradycardia and return to baseline hemodynamic after stabilization [24]. As with our previous study [4], the chosen dose range of our study seems to be safe in terms of mean arterial pressure and heart rate, as they were similar between the studied drugs, and showed that the hypotensive events could all be rapidly corrected.

In terms of opioid sparing effect and respiratory function, we could not observe any significant favourable influence of dexmedetomidine over the conventional use of midazolam, which may be attributable to the following. The chosen M regimen has been used and adjusted in our institution over the past 5 years for PTA to provide safe conscious sedation, which yielded acceptable patient satisfaction as well.

The limitations of the current study are as follows. Although there are solid experimental backgrounds, we did not measure markers of oxidative stress or inflammation, and thus, we can only speculate about the favourable influence of dexmedetomidine on post-reperfusion pain. Also, the sample size may be insufficient for validating our secondary endpoints, especially in terms of pain scores as they showed only statistical trends towards being lower in the DR group. Lastly, due to the nature of the disease, the inclusion of male patients was predominant, limiting the extrapolation of these results to female patients.

In conclusion, MAC for a high-risk group requires special attention balancing the safety and the patients' satisfaction. Also, a proper anaesthetic regimen should be tailored to cover the disease- and procedure-specific pain characteristics that are unique to patients with PAD undergoing PTA. In line with these needs, the current study provides primary evidence that the use of dexmedetomidine in conjunction with remifentanil may be a safe option that provides excellent patients' satisfaction while potentially attenuating postprocedural pain as well.

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