The effect of dexmedetomidine on blood pressure and recovery conditions of intellectually disabled adults: A double-blinded randomized clinical trial

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Abstract

Purpose. Providing dental treatment for intellectually disabled patients is usually performed under general anesthesia. This randomized double-blinded parallel clinical trial study aims to evaluate the effect of dexmedetomidine on the blood pressure and recovery conditions of these patients. Methods. Fifty intellectually disabled patients without systemic problems or physical disability were recruited. The anesthetic regimen included 5 mg/kg of sodium thiopental, 0.8 mg/kg of atracurium, and 1-2 mcg/kg of fentanyl; and 100 mcg/kg/min propofol for maintenance. The intervention group received additional 2 mcg/kg/h dexmedetomidine by infusion. The control group received equal amount of 0.9% saline. Patients' blood pressure, duration of anesthesia and recovery, types of dental treatments and agitation levels in recovery were recorded. Results. Systolic blood pressure fluctuated in control group (P = 0.032 between 15 and 30 minutes and P = 0.009 between 45 and 60 minutes), while it did not significantly alter in the intervention group (P = 0.942). The diastolic blood pressure did not significantly change neither in dexmedetomidine (P = 0.094) nor in the control group (P = 0.277). Patients' agitation levels were significantly lower in dexmedetomidine group at 15 (P = 0.015) and 30 (P = 0.003) minutes post-operatively. The use of dexmedetomidine did not significantly elongate the stay in recovery (P = 0.194). Conclusion. Dexmedetomidine can be used to improve intra-operative blood pressure stability and to decrease post-operative agitation without lengthening recovery time.

Title Page

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Running title: Dexmedetomidine for mentally disabled

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What is already known about this subject?

1. **Patients with intellectual disability need safe general anesthesia for many therapeutic procedures.**
2. **Dexmedetomidine has been used as an anesthetic adjuvant in different clinical scenarios.**
3. **Dexmedetomidine has shown contradictory effects on patients' hemodynamics.**

What this study adds?

1. **Patients with intellectual disability may experience blood pressure fluctuation during dental treatment under general anesthesia.**
2. **The use of dexmedetomidine administered via infusion helps stabilize patient's blood pressure.**
3. **The intellectually disabled patients experience less post anesthesia agitation when dexmedetomidine is administered during anesthesia.**

Abstract

Purpose. Providing dental treatment for intellectually disabled patients is usually performed under general anesthesia. This randomized double-blinded parallel clinical trial study aims to evaluate the effect of dexmedetomidine on the blood pressure and recovery conditions of these patients.

Methods. Fifty intellectually disabled patients without systemic problems or physical disability were recruited. The anesthetic regimen included 5 mg/kg of sodium thiopental, 0.8 mg/kg of atracurium, and 1-2 mcg/kg of fentanyl; and 100 mcg/kg/min propofol for maintenance. The intervention group received additional 2 mcg/kg/h dexmedetomidine by infusion. The control group received equal amount of 0.9% saline. Patients' blood pressure, duration of anesthesia and recovery, types of dental treatments and agitation levels in recovery were recorded.

Results. Systolic blood pressure fluctuated in control group ($P = 0.032$ between 15 and 30 minutes and $P = 0.009$ between 45 and 60 minutes), while it did not significantly alter in the intervention group ($P = 0.942$). The diastolic blood pressure did not significantly change neither in dexmedetomidine ($P = 0.094$) nor in the control group ($P = 0.277$). Patients' agitation levels were significantly lower in dexmedetomidine group at 15 ($P = 0.015$) and 30 ($P = 0.003$) minutes post-operatively. The use of dexmedetomidine did not significantly elongate the stay in recovery ($P = 0.194$).

Conclusion. Dexmedetomidine can be used to improve intra-operative blood pressure stability and to decrease post-operative agitation without lengthening recovery time.

Manuscript text:

Introduction

Providing dental treatments for people with intellectual disabilities is challenging. This is due to the lack of proper oral hygiene, higher prevalence and severity of dental caries along with periodontal problems. Such conditions are mainly caused by a lack of physical functional skills, failure in understanding the importance of oral hygiene maintenance, the complex systemic status of these people and regular medication use. In addition, dental fear and anxiety usually lead to delay in seeking dental treatments. [1] Behavioral control methods cannot be effectively used in the intellectually disabled people; therefore, dental treatments are usually performing under general anesthesia. There is also the advantage of performing the necessary dental procedures in just one session instead of multiple consecutive sessions. [2]

For patients undergoing ambulatory dental treatments, a rapid and safe recovery with minimal post-operative complications is desirable given that treatment under general anesthesia is completed in a relatively short time and patients are normally discharged the same day. It is also important that patients have a smooth emergence without experiencing agitation or pain. Despite many efforts to improve recovery conditions, some patients with intellectual disabilities still experience considerable post-anesthesia complications. [3] Multiple factors including the anesthetic medication regimen used, type of treatment and the underlying diseases play a key role in recovery conditions and post-anesthesia complications. [4]

Dexmedetomidine as an adrenoceptor agonist acts highly selectively for alpha-two receptors and acts 1620 times more on alpha-two than alpha-one receptors. For the purpose of comparison, clonidine, which is also a selective alpha-two agonist, has only 220-fold affinity for the alpha-two versus the alpha-one receptors. [5] The main side effect reported for this drug is prolonging the recovery time and altering haemodynamics in forms of both hypertension and hypotension along with bradycardia due to vasoconstriction, parasympathetic activation mediated by baro-reflex and sympatholysis. [5, 6]

Most studies on the use of dexmedetomidine in dentistry have examined its sedative properties. There are very few studies on the use of dexmedetomidine in dentistry for general anesthesia, most of which are related to pediatric dentistry. [7] However, there are no studies evaluating the effectiveness of this drug on haemodynamics and the recovery conditions of intellectually disabled adults for ambulatory dental treatments. Therefore, this study aimed to examine the effects of dexmedetomidine on patients' blood pressure, recovery length and agitation for the adult intellectual disabled in dentistry under general anesthesia.

Methods

This study was a prospective double-blinded parallel randomized clinical trial conducted at Torabinejad Dental Hospital in School of Dentistry, Isfahan University of Medical Sciences, Iran. The protocol to this study was submitted under the code of IRCT20190626044013N2 in the Iranian Registry of Clinical Trials. This study was registered at Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran under registration code: IR.MUI.RESEARCH.REC.1399.763 at 3 March 2021.

This trial was conducted in complete accordance with the Declaration of Helsinki. [8] Power analysis showed that a sample size of 25 in each group was needed for a significance level set at 0.05 and a power of 80%. The participants (aged 10-50 years) were intellectually disabled without systemic problems or physical disability, who needed to receive dental services under general anesthesia. The patients were considered to have intellectual disability if they had problems in both intellectual and adaptive functioning in conceptual, social and practical domains according to American Psychiatric Association. [9] The exclusion criteria were patients who used anti-depressants, anti-convulsive, anti-psychotic, anti-hypertensive or tranquilizer drugs. Patients suffering from hepatic disorders, allergic to soybeans or eggs and those with a body mass index (BMI) equal to or more than 40 were also excluded. Using the simple sampling method, 50 patients referring to the dental hospital center were included in the study. An informed consent was obtained from the patient's guardian before enrolment in the study.

Patients were randomly divided into intervention and control groups using a computer-generated sequence with an allocation ratio of 1:1. The patients were blind to their category, and their allocation was concealed

in sequentially numbered, opaque sealed envelopes prior to the beginning of procedure. Patient enrolment and intervention assignment was carried out by a person unaware of the content of envelopes. In both groups, the drug regimen used to induce anesthesia was 5 mg/kg of sodium thiopental (VUAB Pharm Inc, Roztoky, Czech), 0.8 mg/kg of atracurium (Caspian Tamin, Rasht, Iran), and 1-2 mcg/kg of fentanyl (Aburaihan Pharmaceutical, Tehran, Iran), and maintenance was achieved with propofol (Dangkook Pharm, Choong Cheong Book-Do, Korea) at a rate of 100 mcg/kg/min. After the induction of anesthesia, the intervention group received additional doses of dexmedetomidine (Exir Pharmaceutical Co, Borujerd, Iran) by infusion with a rate of 2 mcg/kg/h as an anesthetic adjuvant until the end of anesthesia. For the control group, equal amounts of 0.9% saline were administered as placebo.

Patients' demographic information was recorded before the procedure. During the anesthesia, the patient's systolic and diastolic blood pressures for every 15 minutes, the duration of anesthesia, and the type and number of dental treatments performed were recorded. If a patient had pain or restlessness in recovery, the relevant symptoms were recorded and analgesia was prescribed as per need. The Richmond Agitation Sedation Scale (RASS) was used to assess patients' agitation levels in the recovery. [10] The recovery time for each patient was recorded before they got discharged. Patients were discharged only after they scored at least 9 in the Post Anesthesia Discharge Scoring System. Assessments were done by a person who was blind to the intervention, and the obtained data were analyzed by independent t-test, repeated measures analysis of variance (ANOVA), LSD post-hoc and Mann-Whitney tests using SPSS (Clarivate Analytics) version 23 software.

Results

In this clinical trial study 50 patients were randomly allocated into intervention (n =25) and control (n =25) groups. Fig 1 shows the flow diagram of patient enrolment. The enrolment started in May 2021. The male/female ratio was 1:1. The mean ± SD ages of the control and intervention groups were 29.04 ± 9.06 and 28.40 ± 9.32 years, respectively, with no statistically significantly difference between the two groups (P = 0.807). The mean ± SD durations of dental procedure under general anesthesia were 91.8 ± 30.6 and 87.6 ± 38.52 minutes in the control and intervention groups, respectively. The anesthesia duration between control and intervention groups was not statistically significantly different (P = 0.670). All 50 patients successfully completed this trial and no missing data were present for the analysis. No adverse events or unintentional side effects were observed in the participants.

Table 1 shows the means and standard deviations of different dental procedures performed in the control and intervention groups. The procedures included six different types of: scaling and root planing (SRP), restoration, pulpotomy, root canal therapy (RCT), simple extraction and surgical extraction of the teeth. No statistically significantly difference was present between the two groups in any treatment types or the total of treatments done (P values presented in Table 1).

Table 2 presents the means and standard deviations of systolic and diastolic blood pressures before the treatment and with 15-minute intervals during the treatment. Repeated measures ANOVA was used to evaluate blood pressure changes during the anesthesia. No statistically significantly change was observed in the dexmedetomidine group (P=0.942), while statistical difference was observed in the control group (P =0.001). LSD post-hoc showed statistical difference between 15 and 30 minutes (P = 0.032) and between 45 and 60 minutes (P = 0.009) during anesthesia in the control group. The diastolic blood pressure did not significantly change neither in dexmedetomidine (P = 0.094) nor in the control group (P = 0.277) during anesthesia.

Regarding recovery duration, a mean ± SD of 85.60 ± 29.52 and 98.0 ± 36.63 minutes was recorded for the control and intervention groups respectively, which were not significantly different (P = 0.194).

The patients' agitation scores based on RASS in different time intervals is presented in Fig 2. The Mann-Whitney test showed that the degree of postoperative agitation between the control and study groups was significant at 15 minutes (P = 0.015) and 30 minutes (P = 0.003), while it was not significant at 45 (P = 0.1) or 60 minutes (P = 0.118) in the recovery.

Discussion

Although most dental treatments are performed in the office without the need for sedation or general anesthesia, some adult patients with inadequate cooperation due to intellectual disabilities or those with high levels of fear may require general anesthesia. Anesthesia for outpatient dental treatments should be followed with a quick and safe recovery with minimum post anesthesia complications. Therefore, choosing the right anesthetic drug is of paramount importance. As most of the adult patients who are candidate for dental treatment under general anesthesia are intellectually disabled, it is vital to study the effects of anesthesia on these patients. [11] The main concerning complications of general anesthesia in these patients include cardiovascular problems. A wide range of cardiovascular problems including extreme alterations in heart rate, cardiac output, myocardial functioning as well as arrhythmias can complicate the anesthesia and treatment procedures. In addition to complete pre-operative medical history taking and perioperative monitoring of blood pressure, ECG, pulse oximetry and management of anxiety both pre-operation and post-operation is vital to decrease cardiovascular complications.

Dexmedetomidine is a highly specific alpha-two receptor agonist with sedative, analgesic, and anxiolytic properties. Considerable attention has been given to this drug in recent years because, unlike other sedatives, it does not cause respiratory depression. [12] The mechanism of action of this drug is related to its binding to central and peripheral alpha-two adrenoreceptors. When binding to the adrenoreceptors located in the pons, sedative and anxiolytic properties are seen. This binding inhibits adenyl cyclase enzyme and, consequently, reduces the production of cAMP. It also promotes changes in ion channels, which ultimately inhibit the release of norepinephrine. This drug is used effectively both before the induction of anesthesia as a prodrug and during anesthesia to control pain throughout and after the procedure. It is also used to reduce the activity of the sympathetic system during the induction of anesthesia and to maintain a stable hemodynamic profile. Moreover, it has also been shown that dexmedetomidine can reduce the maximum heart rate by 18%. By increasing the effectiveness of anesthetic drugs, dexmedetomidine can reduce the need for anesthetic drug sodium thiopental by 17-30%. [13]

The results of current study showed that stable systolic and diastolic blood pressures in patients during general anesthesia can be achieved by using dexmedetomidine. Side effects of dexmedetomidine are usually in the form of hemodynamic alterations. However, no significant bradycardia or hypotension requiring intervention was observed due to the dexmedetomidine infusion used in the current study. In fact, a more stable systolic blood pressure was observed in the intervention group. This finding is consistent with previous studies that showed established dexmedetomidine, given by infusion, attenuated hemodynamic stress response in surgical procedures. [14-17] In a study that compared hemodynamics in patients undergoing general anesthesia for laryngeal microsurgery with dexmedetomidine or remifentanil, comparable results were obtained for the two groups. [18] Another study comparing dexmedetomidine and fentanyl for laparoscopic cholecystectomy favored dexmedetomidine for hemodynamic stability. [19] In another study using perilesional infiltration of dexmedetomidine for maxillofacial surgeries under general anesthesia, stable hemodynamics was maintained both during and after operation, whereas the patients in placebo group experienced tachycardia and hypertension frequently. [20] Similarly, in another study investigating intra-cranial operations, the dexmedetomidine group had a considerably more stable hemodynamics than patients receiving placebo. [21]

A biphasic hemodynamic response following the intravenous bolus administration of dexmedetomidine has been reported in the literature. The bolus administration causes a peak concentration of the drug in the plasma which acts on alpha-two receptors in vascular smooth muscles, increasing vascular resistance and causing peripheral vasoconstriction and hypertension. This is followed by baroreceptor reflex bradycardia. With the decrease in plasma concentration of the drug, vasodilation due to activation of alpha-two receptors in vascular endothelial cells begins. The combination of catecholamine release inhibition, increased vagal activity and vasodilation initiates the hypotensive phase. This phenomenon is not as marked with infusion administration of dexmedetomidine. [5] Although no previous study was found on hemodynamics with dexmedetomidine in dental treatments, it seems that dexmedetomidine, if administered properly, can be used

without causing hemodynamic instability in different clinical scenarios.

As for the recovery time, the use of dexmedetomidine did not statistically significantly increase the patients' stay. A meta-analysis on the use of dexmedetomidine with sevoflurane in children undergoing general anesthesia demonstrated a shorter period of stay in post-anesthesia care unit (PACU) with use of dexmedetomidine. [22] A retrospective cohort study suggested that there was a dose-dependent association between the use of dexmedetomidine and the longer stays in PACU. This finding was explained with respect to long acting time of dexmedetomidine which is of importance only in short procedures. [23] Dexmedetomidine activates central alpha-two receptors (both pre-synaptic and post-synaptic) located in locus coeruleus. This activation induces a level of unconsciousness similar to that observed in natural sleep, which may contribute to delayed emergence in patients. [5] A high inter-individual variability has been observed in pharmacokinetics of this drug for distribution volume and hepatic clearance. [5] This variability can explain the inconsistency present in the literature. The results of the current study suggest that the factors influencing the recovery time for intellectually disabled patients are complicated, and the sole use of dexmedetomidine does not statistically significantly elongate the recovery duration.

Dexmedetomidine has been shown to be effective in reducing the incidence of emergence delirium in children. [12] It has also been effective at reducing agitation in patients who were experiencing symptoms of pre-operative anxiety. [24] According to a systematic review dexmedetomidine relieves postoperative pain and prevents emergence agitation. [25] In the current study, dexmedetomidine had a positive effect on the agitation levels of patients 15 and 30 minutes after entering the recovery. The agitation levels after 45 minutes onward were comparable in both study groups. This finding suggests that the benefit of using dexmedetomidine to control agitation is most prominent during the first 30 minutes of recovery, which is actually the interval that patients are susceptible to experience post-anesthesia agitation the most. In a recent meta-analysis about the effect of dexmedetomidine on the quality of recovery, it was concluded that the anxiolytic and analgesic effects of dexmedetomidine along with its inhibition of stress and inflammation of the surgical trauma lead to higher scores for quality of recovery in adult patients. [6]

An important aspect in conducting clinical trials is to avoid confounding factors as much as possible via randomization. The strength of our study was complete adherence to protocols needed to avoid introduction of any biases or confounders into the study. The demographic profile of patients, duration of treatment and types of dental treatments were not statistically different between the two groups, minimizing the need to adjustments in data analysis. Known factors impacting on dexmedetomidine pharmacokinetics are obesity, hepatic impairment and possibly cardiac disorders, all of which were avoided in the recruitment process. [5]

One of the limitations of the current study was the unfeasibility of using a Visual Analogue Scales to quantitatively measure the severity of pain in the recovery due to the intellectual disability of the patients. Furthermore, progressive postoperative forgetfulness is suggested to be one of the side effects of using dexmedetomidine. However, it was not assessed in the current study either due to the intellectual conditions of the participants. Nevertheless, more comprehensive studies on use of dexmedetomidine in patients with intellectual and physical problems will provide better understanding of different uses of this drug.

Conclusions

Within the limitations of this study it was concluded that the use of dexmedetomidine as an adjuvant to anesthetic drug for intellectually-disabled patients improve intra-operative hemodynamics and reduces post-operative agitation levels without lengthening the recovery period.

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Conflict of Interest: None

Data availability: Research data are not shared.

Authors Contribution

Conceptualization: Mahtab Tabesh, Nasser Kaviani, Ali Akhavan, Ghader Feizi**; Methodology:** Mahtab Tabesh, Nasser Kaviani**; Investigation:** Nasser Kaviani, Ali Akhavan, Ghader Feizi**; Resources:** Ali Akhavan, Ghader Feizi **; Formal analysis:** Mahtab Tabesh **; Writing – original draft preparation:** Mahtab Tabesh **; Writing – review and editing:**Nasser Kaviani, Ali Akhavan, Ghader Feizi **; Supervision:** Nasser Kaviani **; Project administration:** Mahtab Tabesh **; Funding acquisition:** Nasser Kaviani, Ali Akhavan

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Tables

Table 1: Mean and SD of different dental treatments performed in control and study groups

treatment	Mean ± SD	Mean ± SD	P value
	control (n = 25)	Dexmedetomidine (n = 25)	
Pulpotomy	0.0±0	0.08±0.40	0.327
Restorative	3.52±2.7	3.80±2.80	0.721
Surgical extraction	0.40±0.82	0.28±0.89	0.622
SRP	0.12±0.33	0.04±0.20	0.308

treatment	Mean ± SD	Mean ± SD	P value
RCT	2.44±2.60	2.48±2.86	0.959
Simple extraction	3.52±5.19	3.12±6.49	0.753
total	10±3.94	9.68±5.44	0.813

Table 2: Mean and SD of blood pressures before and during treatment in control and study group

Time	Systolic Blood Pressure (mmHg)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
	mean±SD	mean±SD	mean±SD
	Control	dexmedetomidine	Control
Baseline	127±20	129±19	72±7
After 15 minutes	115±16	109±14	71±6
After 30 minutes	118±17	109±15	71±5
After 45 minutes	115±14	108±15	72±6
After 60 minutes	119±15	110±14	71±5

Figure legends

Fig 1 The flow diagram of patient enrolment, treatment and follow-up

Fig 2 The frequency of each RASS score in control and intervention groups in different time intervals during recovery phase: a) after 15 minutes, b) after 30 minutes, c) after 45 minutes, d) after 60 minutes.