# Efficacy of ketamine, propofol, and dexmedetomidine for anesthesia in electroconvulsive therapy in treatment-resistant major depressive disorder patients: a double-blind randomized clinical trial

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## Abstract

Electroconvulsive therapy (ECT) is one of the therapeutic opportunities for patients with psychological disorders when they may decline to take medication. We sought to systematically compare the anesthetic efficacy of ketamine, propofol, and dexmedetomidine for electroconvulsive therapy in treatment-resistant major depressive disorder patients. This double-blind trial enrolled treatment-resistant major depressive disorder patients ($n$ = 85) who had been hospitalized for ECT in the Amir Kabir Hospital's psychiatric ward (Arak, Iran). The ketamine, propofol, and dexmedetomidine groups received a dose of 0.2 μg/kg ketamine, 1.5 mg/kg propofol, and 0.8 mg/kg dexmedetomidine, respectively. In all intervention groups, 10 mL of interventional drugs was injected intravenously for 10 minutes, and in the placebo group, 10 mL of normal saline was given over the same period. The dexmedetomidine group's blood pressure was revealed comparatively lower at all times. Dexmedetomidine-treated patients showed their marked satisfaction, while those treated with propofol had shorter recovery time, shorter seizure duration, and shorter time to achieve an Aldrete score of 9–10 and increased relaxation, and next dexmedetomidine produced deeper relaxation. Propofol could shorten recovery time and seizure duration, and enhance relaxation, while dexmedetomidine was associated with higher patient satisfaction. Considering that any anesthetic which does not shorten seizure duration may serve efficiently for ECT and that ketamine-treated patients had more prolonged seizure duration, the preferred drug can hence be considered from various angles, thereby offering anesthetic agents with highly favorable efficacy in treatment-resistant major depressive disorder patients needing ECT. The drug choice thus depends on physical conditions, underlying diseases, and psychiatrist consultation.

**Key words:** analgesics; depressive disorder; dexmedetomidine; electroconvulsive therapy; ketamine; propofol; psychological disorders; seizure

**doi:** 10.4103/2045-9912.350860
**How to cite this article:** Modir H, Mahmoodiyeh B, Shayganfard M, Abdus A, Almasi-Hashiani A. Efficacy of ketamine, propofol, and dexmedetomidine for anesthesia in electroconvulsive therapy in treatment-resistant major depressive disorder patients: a double-blind randomized clinical trial. Med Gas Res. 2023;13(3):112-117.
**Funding:** The study was supported by Arak University of Medical Sciences.

## Introduction

Electroconvulsive therapy (ECT) has successfully been highlighted as one therapeutic opportunity for patients with schizophrenia and major depressive disorder (MDD) when they may decline to take medication.[1] The procedure applies scheduled electrical stimulation to the central nervous system to initiate seizure activity.[2] Nowadays it has been employed for treating severe mental illnesses, chiefly, MDD, bipolar mood disorders, schizophrenia, and catatonia.[1,3] Electrical stimulations produce a generalized tonic seizure lasting nearly 10 seconds, followed by a generalized clonic seizure for a varied period ranging from a few seconds up to more than 1 minute. Anesthetics for inducing anesthesia during ECT affect the severity of hemodynamic changes stemming from parasympathetic and sympathetic discharge and seizure duration, as one key determinant of the effectiveness of treatment, while reducing physical and psychological trauma.[4] On the other hand, they indirectly affect ECT-induced cognitive impairment and patient's outcomes.[1,4,5]

A diverse array of anesthetics are available for anesthesia induction in ECT, including methohexital, thiopental sodium, propofol (PRO), etomidate, ketamine (KET), and benzodiazepines.[1,3-5] Good anesthesia induction for ECT seems to be associated with minimum hemodynamic changes, more rapid recovery time, and fewer complications, with no adverse effects on therapy outcomes. Nowadays, anesthesiologists administer various agents like labetalol, remifentanil, magnesium sulfate, and even dexmedetomidine (DEX) for ECT,[5] while being expected ultimately to induce rapid anesthesia, to provide muscle relaxation, to maintain anesthesia depth, to maintain seizure duration, and to recover fast.[3] They use monitoring techniques, sedatives and muscle relaxants as the common components of the therapy to lessen ECT-induced complications. Post-ECT hemodynamic changes occur sometimes so greatly that they can develop cardiovascular complications and cerebral events, especially in the older adults, which has been a topic issue addressed in many studies.[1,3]

The ideal anesthetic agent for ECT is fast-acting, does not interfere with seizure duration and recovery time, and besides,

it contributes to managing the patient's hemodynamic status.[6] For this purpose, various drugs have been administered like remifentanil[7] and α2-adrenoceptor agonists,[6] amongst which DEX is believed to be an adrenoceptor agonist, sedative and antihypertensive agent and if administered, it contributes to lessening heart rate (HR), systemic vascular resistance, and blood pressure (BP).[8] It has developed as a drug to induce general anesthesia with a central sympatholytic effect, contributing to maintaining the patient's hemodynamic status. DEX has potent anesthetic and analgesic properties, reducing the need for opioids, complications, and stress response, and improving the quality of recovery.[1,8] The anesthetic ability of DEX seems to be unique and brings about a mild cognitive impairment facilitating straightforward communication between the medical staff and the patient.[9]

KET is an anesthetic derivative of phencyclidine and possesses various effects on the central nervous system. It stimulates the sympathetic nervous system in the limbic system while suppressing waves in the cortex and thalamus.[10,11] Several studies have repeatedly reported the effect of KET on the ECT-induced seizure duration, among which anesthesia based on KET can appear to increase total seizure energy in patients being treated with ECT, compared with that based on methohexital, and besides, the use of KET in ECT-resistant patients has been supported.[12-14]

PRO is an intravenous anesthetic and an excellent general anesthetic at higher doses, whereas it is considered to be a useful adjunct to conscious sedation. It is a hypnotic agent and can weaken the cardiovascular and respiratory systems in a dose-dependent manner. PRO is known to possess direct antiemetic effects, however, like benzodiazepines, has no analgesic effects[15,16] and is used for conscious sedation and hypnosis to induce and maintain conscious sedation. Its pharmacokinetics makes it suitable for conscious sedation. The main advantages of this drug are fast-acting, lacking active metabolites, and rapid hepatic clearance after intravenous administration.[6,16]

A trial on the effectiveness of DEX on ECT[17] reported that DEX used before anesthesia induction can affect hemodynamic responses but not seizure duration.[17] Mohseni et al.[18] reported that KET may be a good choice for anesthesia during ECT, thanks to its effects on prolonged seizure duration, not so noticeable hemodynamic effects, and reduced post-ECT-related complications, compared with sodium thiopental. Another study by Wang et al.[19] confirmed that the seizure energy index and seizure duration were higher and longer in the KET alone and combination groups than in the PRO group, suggesting that PRO plus KET could be the first choice for anesthesia in patients with depressive disorder.[19]

Considering that no trial has hitherto fully explored and compared the anesthetic efficacy of three drugs for treatment-resistant MDD patients undergoing ECT and that previous studies evaluating one or two drug treatments produced different outcomes, this clinical trial was outlined to compare KET, PRO, and DEX for anesthesia in electroconvulsive therapy in patients with treatment-resistant MDD. It can be introduced for ECT if the study results here could show the superiority of one or two drugs in improving the patients' condition.

## Subjects and Methods

### Study setting and patients

The double-blinded randomized trial enrolled 68 treatment-resistant MDD patients requiring ECT who were hospitalized in the Psychiatric Ward of the Amir Kabir Hospital (Arak, Iran) from December 2020 to March 2021. Informed written consent (**Additional file 1**) was obtained from each patient and the study protocol was approved by the Ethical Committee of Arak University of Medical Sciences (approval No. IR.ARAKMU.REC.1398.290; January 18, 2020; **Additional file 2**) and Iranian Registry Clinical Trial (registration No. IRCT20141209020258N143; June 21, 2020). This study followed the CONsolidated Standards Of Reporting Trials (CONSORT) guidelines[20] (**Additional file 3**).

**Inclusion criteria:** 18–60 years of age, both sexes, no history of drug use, no pregnancy, no history of cardiovascular diseases (arrhythmia, ischemia, and heart block), no use of beta-blockers, alpha-2 agonists, lack of sensitivity to medications used, a diagnosis of schizophrenia and the absence of contraindications for ECT such as space-occupying lesion of the brain, increased intracranial pressure, and recent myocardial infarction.

**Exclusion criteria:** patients suffering from arrhythmia or life-threatening hemodynamic changes requiring intervention during ECT, those with tonic-clonic seizures lasting less than 25 seconds, and finally those not willing to participate in the study.

### Intervention

The subjects who have already been diagnosed as candidates for ECT, based on a diagnosis by a psychiatrist (BM), as well as those with American Society of Anesthesiologists I–II[21,22] and without cardiovascular, respiratory, and vascular diseases, were randomized by block randomization method into four groups by an anesthesiologist (HM) as depicted in **Figure 1**: DEX ($n$=18), KET ($n$=18), PRO ($n$=17) and placebo (PBO; $n$=17) groups. All subjects were nil per os after midnight before the procedure, and then given 5 mL/kg crystalloid after placing an intravenous line and before anesthesia. We monitored non-invasive BP, electrocardiogram, and pulse oximetry assessment for all subjects from entering the ECT room until transferred to the ward. The DEX, PRO, and KET groups received a dose of 0.2 μg/kg DEX (Exir Pharmaceutical Co., Borujerd, Iran), 1.5 mg/kg PRO (Fresenius Co., Bad Homburg, Germany), and 0.8 mg/kg KET (Rotexmedica Co., Hamburg, Germany), respectively. The interventional drug with a volume of 10 mL in each group was injected intravenously slowly for 10 minutes, and in the PBO group, 10 mL of normal saline was given to patients over the same period.

All subjects received 0.5 mg of atropine (Caspian tamin Pharmaceutical Co., Rasht, Iran) before induction of anesthesia and each anesthetic drug was titrated to loss of consciousness with an infusion of thiopental sodium (Jaber-Pharma Co., Karaj, Iran) at a dose of 1.5–3 mg/kg. Afterward, succinylcholine chloride was administered at a dose of 0.5 mg/kg, and the lung was ventilated with 100% oxygen via a bag-valve mask. Based on the psychiatrist's opinion, a bifrontotemporal electrical stimulation was applied by electrodes positioned on both

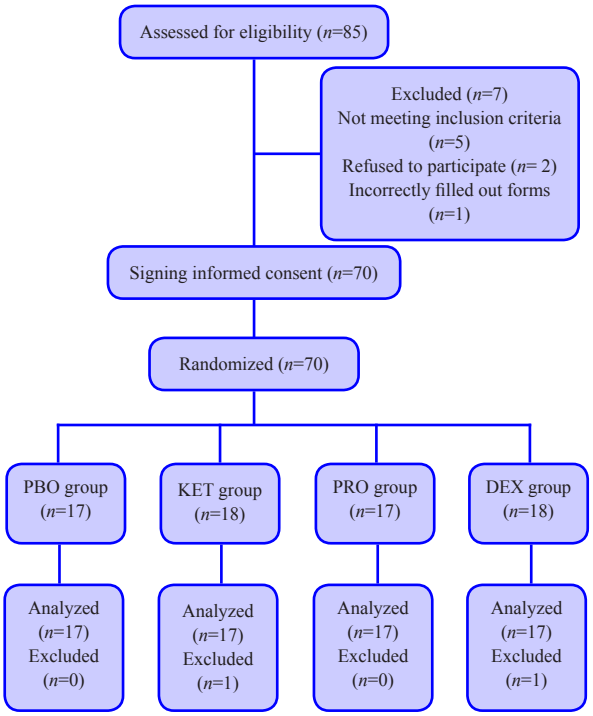


**Figure 1: CONsolidated Standards Of Reporting Trials (CONSORT) diagram showing the flow of the clinical randomized trial.**
Note: DEX: Dexmedetomidine; KET: ketamine; PBO: placebo; PRO: propofol.

sides of the head after anesthesia induction and the subjects received 30–100 joules of electric shock. The subjects entered the recovery room and produced seizures after shocking, to gain the return of adequate spontaneous breathing. Then, an oxygen mask at 5 L/min was put.

### Measurements

As previously stated, the BP, HR, and oxygen saturation of each patient were recorded from the patient's arrival in the shock room (T0), 1 minute (T1), 5 minutes (T5), and 10 minutes (T10) post intervention and every 5 minutes post ECT until transferred to the ward. A modified Aldrete score[23] of 9 out of 10 was a commonly used scale for determining when people can be discharged to the ward and, if achieved, it was recorded as the time for patient transfer to the ward.

Recovery time was defined and recorded as the time interval required from administration of succinylcholine chloride until the subject responds to verbal commands and opens his/her eyes. Moreover, the level of patients' satisfaction was assessed using the satisfaction scale,[23] as follows: 1, happy and calm; 2, no complaints and not bad satisfaction; 3, complaint and moderate satisfaction; and 4, patient's discomfort and unwillingness to be treated in the same technique.1 After being recovered, the agitation was recorded using a 5-point agitation score,[24] as follows: 1, sleeping; 2, awake and calm; 3, irritable and crying; 4, inconsolable crying; 5, severe restlessness, disorientation, wanting to get out of the bed and to stand in the bed, shouting, crying, or mumbling loudly. Moreover, we recorded all side effects, including bradycardia (20% decrease from baseline), hypotension (20% decrease from baseline), decreased oxygen saturation (less than 90%), and other complications such as nausea, vomiting, dizziness, and muscle pain, while taking remedial action if needed. The main outcomes were hemodynamic parameters, agitation and recovery time in patients in each group. Moreover, the seizure frequency and duration were recorded.

The data were measured and recorded by an intern unaware of grouping information, to ensure a double-blind study. The adjuvants for each group were prepared and administered by the anesthesiologist (HM), whereas the subjects were unaware of the group they were in.

### Statistical analysis

Sample size calculation was conducted by considering the difference of agitation score among groups, with a study power = 80% and a type one error = 0.05. Data were analyzed using SPSS version 20 (IBM Corp, Armonk, NY, USA) by one-way analysis of variance and Tukey's *post hoc* test, Chi-square and repeated measurement tests by Greenhouse-Geisser method.

## Results

The enrolled patients were aged 19–50 years, with a mean age of 34.04 ± 7.70 years. There were 36 (53%) males and 32 (47%) females. No statistically significant difference was found in oxygen saturation, HR, and side effects among the four groups studied ($P > 0.05$).

As shown in **Figure 2**, statistically significant differences were observed in BP from 5 to 50 minutes post ECT among the four groups ($P < 0.001$). The repeated measurement test showed that BP was lower in the DEX group at all times compared with the other groups ($P < 0.05$). Nevertheless, there was no significant difference among KET, PRO, and PBO groups.

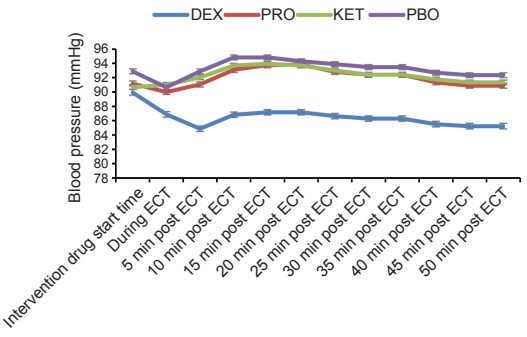


**Figure 2: Effect of ketamine (KET), propofol (PRO), and dexmedetomidine (DEX) on the blood pressure during anesthesia of electroconvulsive therapy (ECT) in treatment-resistant major depressive disorder patients.**
Note: Data are expressed as mean ± SD ($n$ =17 per group) and were analyzed by repeated measurement test. BP was lower in the DEX group at all times after ECT ($P < 0.05$). But the other three groups including ketamine, propofol, and placebo (PBO) groups had similar BP at different times after ECT.

As shown by the results in **Table 1**, statistically significant differences were seen in recovery time, seizure duration, and time to achieve an Aldrete score of 9–10 among the four groups studied, whereas all the times were shorter in the PRO group compared with the other groups ($P < 0.001$). The *post hoc* analysis showed that the recovery time was longer in the three intervention groups than the PBO groups and this time was significantly longer in the DEX group than the PRO and KET groups. Seizure duration and time to achieve an Aldrete score of 9–10 was significantly higher in the DEX, PBO and

KET groups than the PRO group ($P < 0.05$). Nevertheless, the seizure duration was significantly higher in the KET group than the other two intervention groups ($P = 0.023$). Nevertheless, time to achieve an Aldrete score > 9 was significantly higher in the DEX group than the other groups.

As shown in **Table 2**, a statistically significant difference was observed in patients' satisfaction among the four groups ($P < 0.001$), while reporting a higher satisfaction rate with DEX. Based on these results, the rate of happy and calm in the DEX and PRO groups was significantly higher than that in the KET and PBO groups. In addition, more complaints and moderate satisfaction were reported in the KET and PBO groups.

As shown in **Table 3**, a statistically significant difference was found agitation during recovery among the four groups ($P < 0.001$) and the PRO group had increased relaxation, and next DEX offered good relaxation. Agitation during the recovery showed that a higher rate of awake and calm was observed in the DEX and PRO groups, while the higher rate of irritable and crying and inconsolable crying was reported in the KET and PBO groups.

## Discussion

Our results showed that BP was lower in the DEX group at all times, while recovery time, seizure duration, and time to achieve an Aldrete score of 9–10 seemed to be shorter in the PRO group. While DEX was associated with higher patients' satisfaction, the PRO group had increased relaxation, and next, DEX offered good relaxation. The seizure duration was longer in the KET group than in the other group, whereas, in general, PRO shortened the recovery time, seizure duration, and increased relaxation.

PRO is an intravenous anesthetic that is excellent for general anesthesia at higher doses, whereas it induces deep relaxation.[15,16] Besides, it is a hypnotic agent that weakens the cardiovascular and respiratory systems in a dose-dependent manner. PRO has direct antiemetic effects[15,16] and several key benefits, including rapid onset of action, lack of active metabolites and rapid hepatic clearance after intravenous injection.[2,25] On the other hand, DEX is an adrenoceptor agonist, sedative and antihypertensive agent and its infusion reduces HR, systemic vascular resistance, and BP. It is an adjuvant to induce general anesthesia with a central sympatholytic effect, contributing to maintaining the patient's hemodynamic status. It has potent anesthetic and analgesic effects, reducing the need for opioids, complications, and stress response, and improving the quality of recovery. The adjuvant's ability to

**Table 1: Anesthetic effect of ketamine (KET), propofol (PRO), and dexmedetomidine (DEX) during electroconvulsive therapy in treatment-resistant major depressive disorder patients**

| Variable | DEX | PRO | KET | PBO | *P*-value |
|---|---|---|---|---|---|
| Recovery time (min) | 41.58±2.69 | 24.94±3.11 | 35.35±2.93 | 29.70±1.53 | <0.001 |
| Seizure duration (min) | 34.70±3.80 | 28.41±1.62 | 40.63±6.43 | 33.35±2.64 | <0.001 |
| Time to achieve an Aldrete score of 9-10 (min) | 41.58±2.69 | 24.94±3.11 | 35.35±2.93 | 29.70±1.53 | <0.001 |

Note: Data are expressed as mean ± SD ($n$ =17 per each group) and were analyzed by analysis of variance. PBO: Placebo.

**Table 2: Effect of ketamine (KET), propofol (PRO), and dexmedetomidine (DEX) on frequency of satisfaction during recovery from anesthesia of electroconvulsive therapy in treatment-resistant major depressive disorder patients**

| Satisfaction | DEX | PRO | KET | PBO |
|---|---|---|---|---|
| Happy and calm | 12(71) | 11(65) | 2(12) | 0 |
| No complaints and not bad satisfaction | 15(29) | 6(35) | 12(71) | 9(53) |
| Complaint and moderate satisfaction | 0 | 0 | 3(18) | 6(35) |
| Patient's discomfort and unwillingness to be treated in the same technique | 0 | 0 | 0 | 2(12) |

Note: Data are expressed as number (percentage) and were analyzed by Chi-square test. PBO: Placebo.

**Table 3: Effect of ketamine (KET), propofol (PRO), and dexmedetomidine (DEX) on frequency of agitation during recovery from anesthesia of electroconvulsive therapy in treatment-resistant major depressive disorder patients**

| Agitation during the recovery | DEX | PRO | KET | PBO | *P*-value |
|---|---|---|---|---|---|
| Agitation score[b] | 1.71±0.47 | 1.94±0.24 | 2.05±0.71 | 2.58±0.71 | <0.001 |
| Sleeping[a] | 15(29) | 1(6) | 1(6) | 0 | <0.001 |
| Awake and calm[a] | 12(71) | 16(94) | 14(82) | 9(53) | |
| Irritable and crying[a] | 0 | 0 | 2(12) | 6(35) | |
| Inconsolable crying[a] | 0 | 0 | 0 | 2(12) | |
| Severe restlessness, disorientation, wanting to get out of the bed and to stand in the bed, shouting, crying, or mumbling loudly[a] | 0 | 0 | 0 | 0 | |

Note: [a]Data are expressed as mean ± SD and were analyzed by analysis of varience foolowed by and Tukey's *post hoc* test. [b]Data are expressed as number (percentage) and were analyzed by Chi-square test. PBO: Placebo.

produce anesthesia is unique, whereas it causes a mild cognitive impairment that facilitates straightforward communication between the medical team and the patient.[9]

Sannakki et al.[17] undertook a study aimed at the effect of DEX on ECT, in which systolic blood pressure was lower in the DEX group than in the PRO group, while the seizure duration was similar. They also reported that DEX administration before anesthesia had an effect on hemodynamic responses but did not affect the seizure duration.[17]

Their results were consistent with ours: similar seizure duration in the DEX and PBO groups. A study by Moshiri et al.[1] compared DEX with alfentanil for premedication on the seizure duration and recovery time, and hemodynamic responses of subjects, concluding that no significant difference was found in seizure duration, agitation score, and hemodynamic changes among the groups, while the recovery time was significantly shorter in the PBO group and patient satisfaction was reported to be higher in the DEX and alfentanil groups.[1] Our study showed a higher level of satisfaction in the DEX group, as well as a shortened recovery time, seizure duration, and time to achieve an Aldrete score of 9–10 in the PRO group.

Besides, Safari's study[3] tried to assess the effect of DEX on hemodynamic changes, seizure duration, and recovery time in subjects undergoing ECT, in which systolic blood pressure decreased in the PRO and DEX groups, while the recovery time increased in the etomidate and DEX groups. DEX prescription was found to prevent hypertension in patients undergoing ECT, which is consistent with ours. Shams et al.[26] explored the efficacy of ketofol-DEX mixture in ECT on depression and agitation, stating that the mixture prolongs seizure duration, reduces depression and agitation, and provides higher patient satisfaction and acceptable reduction in BP and HR. Their results were consistent with our study, except that here no difference was found in the MPB among the groups.[26] Wang et al.[19] undertook a study exploring the effect of PRO and KET on ECT in patients with depressive disorder, in which the seizure energy index and seizure duration were both higher and longer in the KET alone and combination groups, respectively, than in the PRO group. Their results suggested that PRO plus KET could be the first choice for anesthesia in patients with depressive disorder,[19] which are consistent with our study findings.

Furthermore, ECT with PRO is associated with faster recovery, whereas the hemodynamic changes occur less frequently. PRO seems to be more efficient than thiopental, especially in patients with hypertension.[2] The results of our study are in line with their findings. A study by Mizrak et al.[7] explored the effect of DEX on various ECT variables, including seizure duration, reporting that premedication with low-dose DEX or midazolam before ECT can be highly useful and effective.[7] The results of our study are in line with those of Mizrak et al.,[7] although PRO could shorten recovery time and lessen agitation of the patients.

Overall, PRO could shorten recovery time, seizure duration, and increase relaxation, while DEX was associated with higher patient satisfaction. Considering that any anesthetic which does not shorten seizure duration may serve efficiently for ECT and that KET-treated subjects had more prolonged seizure duration, hence, the preferred drug can be considered from various aspects. Thus, KET, PRO, and DEX can be offered as drugs with good efficacy in treatment-resistant MDD patients needing ECT. The drug choice depends on physical conditions, underlying diseases, and psychological consultation by a psychiatrist.

The small sample size in each group was one of the limitations of this study. Moreover, no longtime follow-up was conducted in this study. So, further studies with larger sample size and more than 1-week follow-up were required.

**Acknowledgements**
The authors would like to express their sincere gratitude to the Valiasr Hospital's Clinical Research Council members for their guidance, as well as to the Research Deputy of Arak University of Medical Sciences for the help and support.

**Author contributions**
Study conception and design: EM, BM, MSH; data interpretation: EM, BM, Ayda Abdus, Amir Almasi-Hashiani; data analysis and manuscript draft: Ayda Abdus, Amir Almasi-Hashiani. All authors have read and approved the manuscript provided.

**Conflicts of interest**
There is no conflict of interest

**Availability of data and materials**
All data generated or analyzed during this study are included in this published article and its supplementary information files.



**Additional files**
***Additional file 1:*** Informed consent template (Persian).
***Additional file 2:*** Hospital ethics approval.
***Additional file 3:*** CONSORT checklist.

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*Date of submission: May 15, 2021*
*Date of decision: August 30, 2021*
*Date of acceptance: December 23, 2021*
*Date of web publication: December 22, 2022*

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 1 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3-4 |
| | 2b | Specific objectives or hypotheses | 4 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 4 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | 4 |
| Participants | 4a | Eligibility criteria for participants | 4 |
| | 4b | Settings and locations where the data were collected | 4 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 4-5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | - |
| Sample size | 7a | How sample size was determined | 6 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | NA |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 4 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 4 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | - |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 4 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 4 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | NA |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 7 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 7 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 4 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | 4 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 4 |
| | 14b | Why the trial ended or was stopped | NA |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | 6 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 6-9 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | 6-9 |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 9 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 11 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 11 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 11 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 4 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 1 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.