Effect of Continuous Infusion of Dexmedetomidine on Blood Loss in Orthognathic Surgery: A Retrospective Study

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Research

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Abstract

Background: Patients with maxillofacial deformities require orthognathic surgeries to correct occlusion. The surgical procedure may lead to massive bleeding, which is associated with hematoma, respiratory obstruction, and asphyxia. Dexmedetomidine has been used in controlled hypotension, and may decrease blood loss in orthognathic surgery. We conducted a retrospective cohort study to evaluate the effect of dexmedetomidine on blood loss in orthognathic surgeries.

Methods: The primary outcome examined was blood loss, and secondary outcomes were postoperative haemoglobin level, intraoperative heart rate, and blood pressure (T0: preoperative; T1: at incision; T2: 30 minutes after incision; T3: 60 minutes after incision; T4: 120 minutes after incision); dose of fentanyl, remifentanil, urapidil, and esmolol; operation time; incidence of allogeneic blood transfusion; crystalloid fluids volume; and colloidal fluid volume.

Results: A total of 1,247 patients were included in the study, and 557 patient pairs were matched via propensity score matching. There were significant decreases in mean blood loss, heart rate at T1–T4, blood pressure at T1, remifentanil and esmolol dosage, and crystalloid fluid volume in the dexmedetomidine group compared with those in the control group. There was also a significant increase in the postoperative haemoglobin level of the dexmedetomidine group.

Conclusions: Continuous infusion of dexmedetomidine can decrease blood loss in orthognathic surgery.

Trial registration number: ChiCTR1800018794 (retrospectively registered)

Name of registry: Chinese Clinical Trial Registry

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1. Background

Patients with maxillofacial deformities require orthognathic surgeries (Le Fort I osteotomy and bilateral sagittal split ramus osteotomy) to correct the inconsistent occlusion [1, 2]. The rich blood supply and deep surgical site of the oral and maxillofacial region often lead to increased bleeding and a limited visual field during the osteotomy of the maxilla, thus increasing the risk posed by surgery. Intraoperative haemorrhage is associated with many postoperative complications, such as hematoma, respiratory obstruction, and even asphyxia [3]. Controlled hypotension has been previously used to decrease bleeding in many maxillofacial surgeries [4, 5]. Many anaesthetic and vasoactive drugs have been used successfully to achieve controlled hypotension [6]. Dexmedetomidine is a potent, highly selective α_2-adrenoceptor agonist that may provide anti-sympathetic analgesia and sedation without respiratory depression [7], and it has been successfully used for controlled hypotension in other surgical procedures [8].

The sedative and analgesia-sparing effects of dexmedetomidine are associated with its effects on the central nervous system in the locus coeruleus and spinal cord dorsal horn neurons [9]. Dexmedetomidine is an α_2-adrenoreceptor agonist. It primarily inhibits norepinephrine release and causes attenuation of excitation in the central nervous system [10]. Binding of postsynaptic receptors by α_2-agonists leads to inhibition of sympathetic activity, which decreases the blood pressure (BP) and heart rate (HR), and results in sedation [11].

This retrospective cohort study aimed to determine the efficacy of dexmedetomidine for managing intraoperative blood loss, perioperative hemodynamics, anaesthetic drug requirements, the incidence of blood transfusion, and length of hospital stay in orthognathic surgeries.

2. Materials And Methods

2.1 Study design

The study is registered at Chinese Clinical Trial Registry (ChiCTR1800018794). Ethical approval (SH9H-2019-T244-2) was obtained from the Shanghai Ninth People's Hospital Research Ethics Committee. We conducted a retrospective cohort study on patients who underwent orthognathic surgeries between March 2017 and August 2018. Institutional review board approval was obtained before the initiation of this study. Patients with a complete medical history and surgical records were included if they were over 18 years old and underwent elective orthognathic surgery. Patients were excluded from the analysis if they had a history of any of the following: allergies to intraoperative-related drugs, heart-related diseases (New York Heart Association class III or higher), severe pulmonary disease (asthma, chronic obstructive pulmonary disease), or severe liver and kidney dysfunction. Each controlled hypotension strategy is different, and there is currently no unified standard strategy for controlled hypotension. Indications for dexmedetomidine include tracheal intubation and sedation during mechanical ventilation for patients undergoing general anaesthesia, and the administration of dexmedetomidine depends on the judgement of senior anesthesiologists. Patients treated with continuous dexmedetomidine were allocated to the dexmedetomidine group, while patients treated without continuous dexmedetomidine were allocated to the control group.

2.2 Anaesthesia procedures and perioperative medication

Upon arrival in the operating room, HR, BP, and oxygen saturation were monitored by electrocardiography, non-invasive BP monitoring, and pulse oximetry, respectively, before an intravenous cannula was inserted. Induction of anaesthesia was similar in every patient, comprising the intravenous administration of 2 mg midazolam, 2–4 μg/kg fentanyl, 1.5–2.5 mg propofol, and 0.15–0.2 mg/kg cisatracurium. Patients underwent endotracheal intubation, invasive BP monitoring, and deep-vein catheterisation during anaesthesia induction. According to the requirements of the surgeon, most patients underwent acute normovolemic hemodilution (ANH) after anaesthesia and before the beginning of the main steps of surgery [12]. Patients in the dexmedetomidine group were given a 0.5–1-μg/kg loading dose of

dexmedetomidine, and 200–400 mL autologous blood was rapidly extracted before incision. Crystalloid liquids were simultaneously infused to patients to supplement the circulating blood volume, dilute the blood, and reduce the loss of visible blood components during surgery. The extracted autologous blood was transfused back to patients before the end of the operation. This has been reported to be an efficacious, safe, and protective method to reduce the concentration of circulating erythrocytes with minimal effects on clotting factors and platelets [13, 14].

At the beginning of the operation, controlled hypotension was administered, and vital signs were closely monitored. Each patient received 4–8 mg/kg/h propofol and 6–18 μg/kg/h remifentanil intravenously, and 2–3% sevoflurane via inhalation. Patients were given 0.1 mg fentanyl before incision and later again if necessary. Patients in the dexmedetomidine group received continuous dexmedetomidine at 0.2–0.5 μg/kg/h. Narcotic drugs and analgesics, including dexmedetomidine, were initially infused 10 min before incision. Mean arterial BP was controlled between 50–60 mmHg. If mean arterial BP was too high, 5 mg urapidil or 5–10 mg esmolol was used. If mean arterial BP was < 50 mmHg, 6 mg ephedrine was used. If a patient was bradycardic during the operation, the infusion of dexmedetomidine was stopped and the patient was excluded from the study. Patients were given 0.5 g tranexamic acid after incision. Allogeneic blood transfusion was performed if necessary, according to the experience of the surgeon and the anesthesiologist. Several clinical measures were used to indicate allogeneic blood transfusion, including haemoglobin < 70 g/L, haematocrit < 30%, and blood loss > 15% of estimated blood volume [15]. In addition, the anesthesiologist and surgeon communicated and arrived at a consensus before the allogeneic transfusion was performed. Administration of all narcotic drugs and analgesics, including dexmedetomidine, was discontinued 15 to 30 min before the end of the operation. When the operation was nearing completion, the patients' BP would be increased to the normal level.

2.3 Data collection

Study data were obtained from intraoperative records and the electronic medical record. The primary outcome was intraoperative blood loss. The secondary outcomes were postoperative haemoglobin (patients who received allogeneic blood transfusions were excluded); intraoperative HR and BP (both measured at five points: T0, preoperative; T1, at incision; T2, 30 min after incision; T3, 60 min after incision; T4, 120 min after incision); dosage of fentanyl, remifentanil, urapidil, and esmolol; operation time; incidence of allogeneic blood transfusion; crystalloid fluid volume; and colloidal fluid volume.

A standard operating procedure (SOP) was established to train relevant researchers, research assistants, and statistical analysts. The researcher completed the case report form (CRF) according to the SOP. Two researchers independently entered the data, and the research assistant checked and generated the data query forms (DQF). If the research data was lost in the electronic database, the researchers went to the medical history room to retrieve the paper medical history data for verification. Problems in DQFs would be modified and resolved after discussion. Once the modification was complete, data was locked and passed to the statistical analyst.

2.4 Data analysis

Propensity score matching (PSM) was introduced to reduce bias due to confounding factors, which might affect surgical decision-making in patients with maxillofacial deformities. Confounding factors included age, height, weight, sex, preoperative haemoglobin, prothrombin time, activated partial thromboplastin time, and ANH. Patients who underwent orthognathic surgeries were matched at a 1:1 ratio with a caliper width equal to 0.01, resulting in the same number of patients in both groups. The t-test was used for parametric scale variables. Scale variables were tested for normality with the Kolmogorov-Smirnov test. The chi-square exact test was used for nominal variables. Statistical analyses were performed using SPSS version 25 for Windows (IBM, Armonk, NY). Differences between the two groups were expressed as difference in means, standard deviation (SD), mean difference (MD), or odds ratio (OR) with 95% confidence intervals (CI). Statistical significance was defined as a p-value < 0.05.

3. Results

Initially, 1,252 patients were identified for analysis in the defined study time period based on the inclusion criteria. After the researchers checked the medical records, five patients were excluded because infusions of dexmedetomidine were discontinued during operations. A total of 1,247 patients were finally included for analysis. All patients were classified as American Society of Anaesthesiologists class I–II. Dexmedetomidine was used continuously in 560 patients, and they were allocated to the dexmedetomidine group. Dexmedetomidine was administered at a maintenance dose of 0.2–0.5 μg/kg/h. Dexmedetomidine was never used in 687 patients, and they were allocated to the control group. PSM was conducted to randomise and control variables, and 557 pairs of patients who underwent orthognathic surgeries were matched. No statistically significant differences were noted at baseline between the PSM-adjusted groups. The study process is shown in Fig. 1. Baseline patient characteristics are shown in

Table

baseline patient characteristics after PSM

Variable	Dexmedetomidine group	Control group	Adjusted P Value
number	557	557	/
Age (y), mean ± SD	23.70 ± 4.36	23.49 ± 4.27	0.411
Height (cm), mean ± SD	166.63 ± 8.65	166.40 ± 8.00	0.754
Weight (kg), mean ± SD	59.81 ± 11.68	58.91 ± 11.13	0.104
Gender (M/F)	205/352	185/372	0.209
Preoperative hemoglobin (g/L), mean ± SD	129.49 ± 14.87	128.42 ± 14.50	0.272
PLT ($\times 10^9$/L), mean ± SD	240.42 ± 47.89	239.72 ± 55.35	0.444
PT (s), mean ± SD	11.40 ±0.92	11.37 ±0.81	0.920
APTT (s), mean ± SD	28.35 ± 2.38	28.19± 2.34	0.127
ANH(mL), mean ± SD	355.30 ± 128.61	350.45 ± 133.52	0.459
PSM: Propensity Score Matching; SD: standard deviation; BMI: body mass index; PLT: platelet; PT: prothrombin time; APTT: activated partial thromboplastin time; ANH: acute normovolemic hemodilution			

There was a significant decrease in mean blood loss, HR at T1–T4, BP at T1, dosages of remifentanil and esmolol, and crystalloid fluid volume in the dexmedetomidine group. There was a significant increase in postoperative haemoglobin in the dexmedetomidine group. There was no significant difference in operation time, intraoperative HR at T0, intraoperative BP at T0 or T2–T4, incidence of allogeneic blood transfusion, dose of fentanyl or urapidil, or colloidal fluid volume. The results of the primary and secondary outcomes are shown in **Table** .

Table

primary and secondary outcomes after PSM

Variable	Dexmedetomidine group	Control group	95% CI	Adjusted P Value
Blood loss (mL), mean ± SD	667.95 ± 272.25	743.54 ± 295.96	-108.41 to -42.76	< 0.001
Postoperative hemoglobin (g/L), mean ± SD	104.49 ± 14.78	99.21 ± 15.74	3.15 to 7.41	< 0.001
Intraoperative HR (bpm), mean ± SD				
T0	80.75 ± 9.32	80.93 ± 11.00	-1.47 to1.01	763
T1	70.86 ± 11.06	78.16 ± 12.93	-8.78 to -5.82	< 0.001
T2	72.80 ± 11.26	79.44 ± 11.45	-8.00 to -5.28	< 0.001
T3	71.82 ± 10.33	79.45 ± 11.16	-8.89 to -6.36	< 0.001
T4	69.72 ± 10.49	78.34 ± 10.56	-9.89 to -7.35	< 0.001
Intraoperative BP (mmHg), mean ± SD				
T0	86.48 ± 8.39	86.76 ± 8.48	-1.28 to 0.71	0.572
T1	60.26 ± 9.91	62.93 ± 10.75	-3.90 to -1.43	< 0.001
T2	55.89 ± 7.66	56.83 ± 8.64	-1.89 to 0.01	0.051
T3	54.65 ± 5.87	55.15 ± 7.17	-1.24 to 0.26	0.179
T4	56.25 ± 7.93	56.80 ± 8.77	-1.54 to 0.43	0.271
Operation time (h), mean ± SD	3.56 ± 1.11	3.68 ± 1.22	-0.26 to 0.01	0.078
Fentanyl (mg), mean ± SD	0.36 ± 0.07	0.35 ± 0.07	-0.01 to 0.01	0.582
Remifentanil (mg), mean ± SD	1.24 ± 0.45	1.50 ± 0.59	-0.32 to -0.20	< 0.001
Incidence of allogeneic blood transfusion (transfused /not transfused)	32/525	42/515	/	0.229

Crystalloid fluids (mL), mean ± SD	2764.90 ± 526.26	2839.68 ±536.56	-135.90 to -13.65	0.017
Colloid fluids (mL), mean ± SD	386.89 ± 348.10	406.64 ± 376.10	-63.80 to 24.30	0.379
Urapidil (mg), mean ± SD	12.59 ± 5.86	12.26 ± 5.41	-0.35 to 1.02	0.34
Esmolol (mg), mean ± SD	18.06 ± 9.94	25.53 ± 10.87	-8.71 to -6.23	< 0.001
PSM: Propensity Score Matching; MD: mean difference; OR: odds ratio; CI: confidence interval; SD: standard deviation; bpm: beat per minute; ICU: Intensive Care Unit T0: preoperative; T1: at incision; T2: 30 minutes after incision; T3: 60 minutes after incision; T4: 120 minutes after incisi				

4. Discussion

The results showed a significant decrease in the mean total calculated blood loss in the dexmedetomidine group compared to that in the control group. This may have been due to the hemodynamic effect of dexmedetomidine. Continuous infusion of dexmedetomidine led to decreased HR and BP, which was caused by a negative feedback loop of norepinephrine. Recent studies have also suggested that dexmedetomidine can decrease blood loss throughout several different surgical procedures [8, 16]. In previous studies, the surgical field of vision, which significantly affects blood loss, was considered to be directly related to decreased HR [17, 18]. There is evidence that decreasing MAP below 70 mmHg increases intraoperative bleeding due to local vasodilation [19], but decreased HR is strongly correlated with cardiac output, which is associated with operative field of vision [18]. In contrast to α_2 agonists, inhalational anaesthetics lead to vasodilatory effects and reflex tachycardia. Furthermore, opioids are less effective than dexmedetomidine in reducing HR. Decreased mean arterial pressure without controlled HR does not lead to improved visibility or lessened bleeding. In addition, the vasoconstrictive effect of intravenous dexmedetomidine has been demonstrated in animal models [20, 21]. Furthermore, studies have provided evidence that intravenous dexmedetomidine has similar vasoconstrictive effects on human arteries and veins [22]. Contraction of the peripheral vessels caused by intravenous dexmedetomidine would further promote surgical site visualisation and reduction of bleeding. Improved surgical field of vision has been mentioned in other studies [23, 24]. This finding is important since it is closely related to blood loss and ease of operation for surgeons. Unfortunately, because this is a retrospective study, the intraoperative visual field could not be assessed using a numerical rating scale or other quantitative methods. Therefore, we could not verify whether the intraoperative field of vision in orthognathic surgery was improved as in other surgeries. Reduced

bleeding will lead to fewer complications, such as hematoma, respiratory obstruction, and asphyxia, and will further promote the patient's postoperative recovery.

There was a significant increase in postoperative haemoglobin in patients treated with intraoperative dexmedetomidine. Patients who received allogeneic blood transfusions during operations were excluded because the level of postoperative haemoglobin would be affected. Reduced intraoperative blood loss increased levels of postoperative haemoglobin and improved postoperative safety. Postoperative anaemia is associated with dizziness, tinnitus, fatigue, hypoxia, and other side effects [25]. Postoperative acute anaemia is correlated with an increased risk of injury to major organs, such as the brain, heart, and kidney [26], and elevated haemoglobin levels will help avoid these risks.

There was a significant decrease in the intraoperative HR of patients treated with intraoperative dexmedetomidine. The current study also revealed that deliberate hypotension with lower HR could reduce intraoperative blood loss and improve the surgical field [27, 28]. Dexmedetomidine decreases HR [29], specifically causing a 16–30% decrease from baseline at plasma drug concentrations > 1–3 ng/mL [30, 31]. There was a significant decrease in intraoperative BP at T1 in patients treated with intraoperative dexmedetomidine. The decreased BP may be caused by transient elevated plasma concentration, and it might further contribute to reduction of intraoperative blood loss in the early surgical procedure. There was no significant difference in the average arterial pressure at most time points due to human control. The anesthesiologist maintained the target BP level after the mean BP reached the target point. In addition, the requirement for esmolol was decreased because of the effect of reducing HR.

There was no difference in operation time between considered groups. Although the amount of blood loss was reduced by dexmedetomidine, the operation time was not shortened. Similar studies have also shown that dexmedetomidine improves the quality of the surgical field without significantly affecting operation time [8, 32]. No difference in the requirement of fentanyl was observed between the groups, but the remifentanil requirement in the dexmedetomidine group was significantly decreased. Studies have shown that long-term and high-dose use of opioids may produce some side effects, such as hyperalgesia, nausea and vomiting, and emergence agitation [33, 34]. The reduced dosage of remifentanil may help alleviate any hyperalgesia and reduce postoperative nausea and vomiting.

There was no significant difference in the incidence of allogeneic blood transfusion between the groups. This might be due to the low transfusion incidence of this surgical procedure. Most patients who undergo orthognathic surgeries do not need blood transfusion, with the exception of those who experience massive bleeding. Studies have also reported that ANH significantly reduces allogeneic blood transfusion [12, 35].

There was no significant difference in colloidal fluid volume. The decreased blood loss and HR, and intraoperative fluid management strategy led to significantly decreased crystalloid fluid volume. In addition, the dose of crystalloid fluids seemed to be large for an average 3.5-h duration of surgery. This may have been caused by heavy bleeding and ANH. Patients were required to be transfused with a large amount of crystalloid liquids after a predetermined amount of autologous blood was rapidly withdrawn

to supplement blood volume and maintain stable vital signs [36]. This protective measure increased crystalloid fluid dosage.

Although the results are promising, there are some limitations to this study. First, the retrospective nature of this study has inherent limitations and potential interference factors regarding data integrity and homogeneity. However, we have strictly followed the criteria for inclusion and exclusion and have used a rigorous statistical approach to avoid bias. Second, this study was a single-centre retrospective study, which may have led to selection bias. We expanded the sample size to minimise bias. Third, visualisation was pointed out, but it could not be assessed because of the retrospective nature of this study. We plan to conduct further studies to elaborate on this aspect. Fourth, different drugs, including propofol, remifentanil, and sevoflurane, were administered, and this may have affected the accuracy of our conclusions. We used various methods to ensure the reliability of the conclusions, such as expanding the sample size, PSM, and strict data management. Finally, different surgeons use different approaches; thus, the methodology of each operation are different. For example, some surgeons might think that preoperative ANH is necessary, while others might not.

The study showed dexmedetomidine decreases blood loss in orthognathic surgeries, and we plan to conduct a randomized controlled study in the future.

5. Conclusion

Continuous infusion of dexmedetomidine decreases blood loss in orthognathic surgeries. Dexmedetomidine also increases postoperative haemoglobin and decreases intraoperative HR.

Abbreviations

HR: heart rate; BP: blood pressure; ANH: acute normovolemic hemodilution; SOP: standard operating procedure; CRF: case report form; DQF: data query form; PSM: propensity score matching; SD: standard deviation; MD: mean difference; OR: odds ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

The study is registered at Chinese Clinical Trial Registry (ChiCTR1800018794). Ethical approval (SH9H-2019-T244-2) was obtained from Shanghai Ninth People's Hospital Research Ethics Committee.

Consent for publication

The authors declare that they obtain exemption of informed consent from Shanghai Ninth People's Hospital Research Ethics Committee.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Chenyu Jin: Conceptualisation, Methodology, Software, Data curation, and Writing- Original draft preparation. Yu Sun: Visualisation, Investigation, Data curation. Xiang Lv: Supervision, Investigation, Software, Data curation. Hong Jiang: Supervision, Writing- Reviewing and Editing.

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Figures

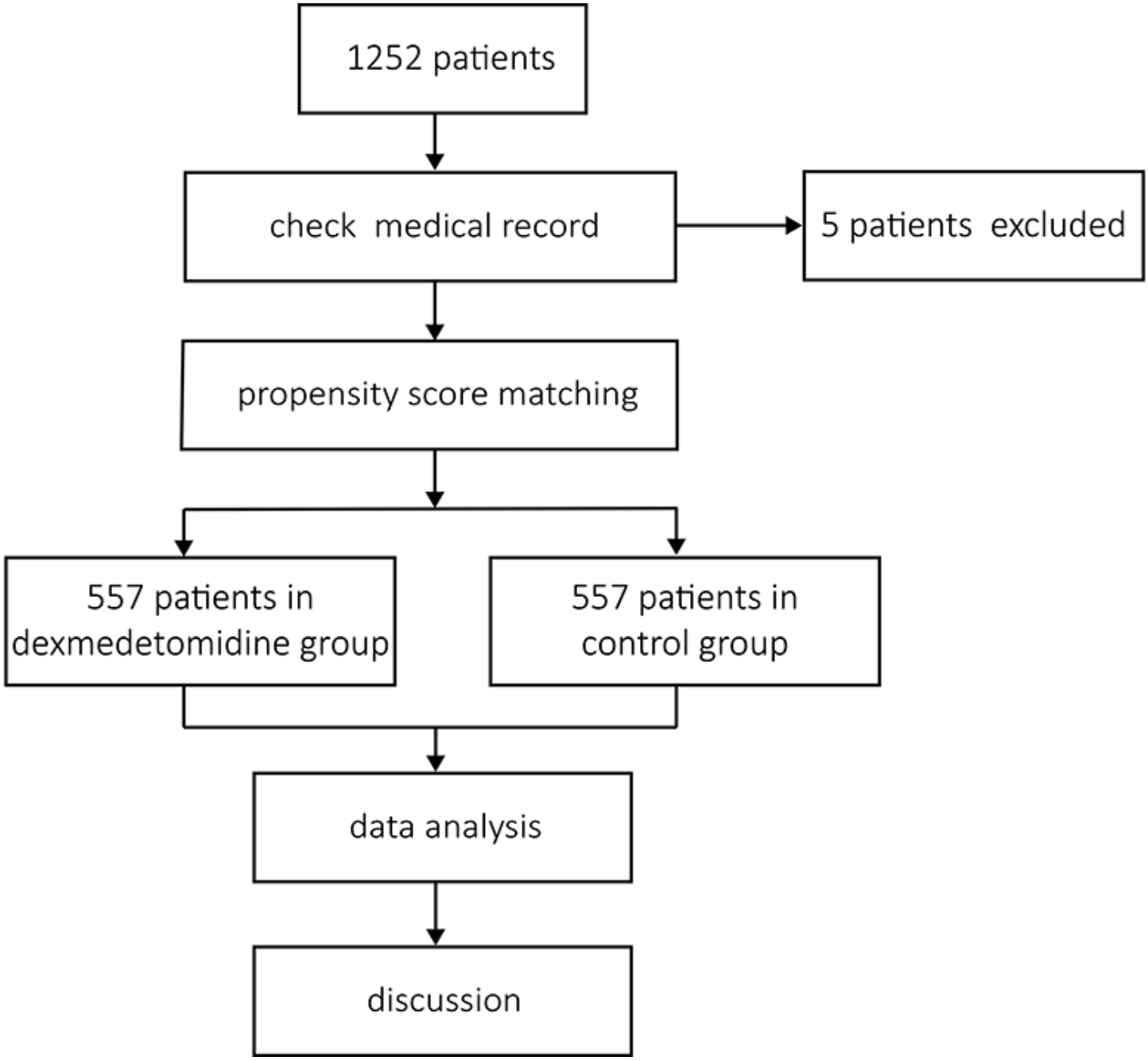

Figure 1

Flow diagram of the study design.