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Randomized controlled trial on effect of different routes of dexmedetomidine on Haemodynamics in patients undergoing saphenectomy under epidural anaesthesia

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The effect of epidural infusion of dexmedetomidine on haemodynamics is unclear. This study aimed to explore the effects of epidural or intravenous infusion of dexmedetomidine on haemodynamics during lower extremity varicose veins surgery (saphenectomy) under epidural anaesthesia. Ninety patients were randomly allocated to three groups: ED group (epidural: 0.59% ropivacaine plus 0.5 μg/kg dexmedetomidine, intravenous: normal saline), VD group (epidural: 0.59% ropivacaine plus normal saline, intravenous: 0.5 μg/kg dexmedetomidine), or NS group (epidural: 0.59% ropivacaine plus normal saline, intravenous: normal saline). The primary outcome was the systolic blood pressure (SBP) at before anaesthesia (T_0) and at 5 (T_1), 15 (T_2), and 30 min (T_3) and 1 (T_4), 2 (T_5), 4 (T_6), 6 (T_7), and 8 h (T_8) after dexmedetomidine infusion. The secondary outcomes were diastolic blood pressure (DBP) and heart rate (HR) at T_{0-8}, plasma norepinephrine (NE), myocardial oxygen consumption (MVO_2) and anesthesia efficacy. Adverse reactions and other general data were also recorded. Compared with those in the NS group, the SBP at T_{3-7} and DBP at $T_{4-5,7}$ were significantly lower in the ED group ($P = 0.008$, 0.001, 0.001, 0.001, 0.038 and $P = 0.017$, 0.006, 0.044, respectively), and the SBP and DBP at T_{1-8} were lower in the VD group ($P < 0.001$, 0.001, 0.001, 0.001, 0.004 and $P < 0.001$, 0.001, 0.001, 0.002, 0.001, 0.001, 0.001, 0.036, respectively). The SBP and DBP at T_{1-2} in the ED group were greater than those in the VD group ($P = 0.021$, 0.01 and $P = 0.001$, 0.011, respectively). The HR at $T_{3-4,6-7}$ was lower in the ED group than in the NS group ($P < 0.001$, 0.021, 0.002, 0.004, respectively). Compared with that in the VD group, the HR in the ED group at T_7 was significantly lower ($P < 0.001$). Anaesthesia efficiency was improved in the ED group compared with VD and NS groups. The incidence of hypotension was lower in the ED group than in the VD group ($P = 0.003$). The combination of 0.5 μg/kg dexmedetomidine and 0.59% ropivacaine for epidural anaesthesia provides more stable haemodynamics with a lower incidence of hypotension and improved efficiency of epidural anaesthesia in patients undergoing saphenectomy.

Keywords Dexmedetomidine, Administration routes, Epidural anaesthesia, Haemodynamics, Anaesthetic effect, Ropivacaine

Compared with other anaesthesia methods, epidural anaesthesia has fewer complications, can promote postoperative recovery and prevent thrombosis[1–5]. Epidural anaesthesia is a commonly performed anaesthesia technique for lower extremity varicose vein surgery in China[6,7]. Nevertheless, epidural anaesthesia is prone to

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imperfect blockade and a slow onset[8], which eventually leads to a decrease in anesthesia satisfaction. To address this issue, anaesthesiologists therefore often prefer to apply more considerable doses of local anaesthetics to achieve the desired anaesthetic effect, but this undoubtedly increases the possibility of local anaesthetic systemic toxicity and haemodynamic fluctuations[9].

Studies have shown that dexmedetomidine combined with ropivacaine for epidural anaesthesia can significantly shorten the onset of anaesthesia and extended the time of anaesthesia, reduce the 50% effective concentration of ropivacaine by approximately 25% and decrease the dosage of local anaesthetics and prolong analgesia time[10]. However, intravenous administration of dexmedetomidine often induces bradycardia, hypotension and other adverse reactions[11]. Clinical cohort studies have shown that intraoperative hypotension during noncardiac surgery is associated with increased mortality due to postoperative complications such as renal insufficiency and myocardial injury due to hypotension[12]. Given that the route of administration of dexmedetomidine with epidural infusion differs from that of intravenous infusion, the influence of the two routes on perioperative haemodynamics may be distinct; however, in the current literature, few studies have focused on the haemodynamic effects of dexmedetomidine epidurals. Thus, we designed this trial to investigate the effects of different routes of infusions of dexmedetomidine on haemodynamics in patients with lower extremity varicose veins under epidural anaesthesia. Considering that intravenous dexmedetomidine causes bradycardia and hypotension, we postulated that epidural dexmedetomidine is haemodynamically more stable than intravenous infusion in patients undergoing saphenectomy.

Materials and methods

Trial design

This protocol was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Ref. 2022ER073-1, 06/12/2021) and registered in the China Clinical Trial Registry (http://www.chictr.org.cn/; registration number: ChiCTR2200060619, 05/6/2022). The purpose of the study was to assess the effects of different routes of infusions of dexmedetomidine on haemodynamics in patients with lower extremity varicose veins under epidural anaesthesia. This clinical trial was conducted between June 8, 2022, and November 30, 2022. All methods were performed in accordance with the Consolidated Standards of Reporting Trials and the Declaration of Helsinki[13]. Written informed consent was obtained from all participants.

Participants

Inclusion criteria: (1) Patients scheduled for saphenectomy under epidural anaesthesia were screened. (2) American Society of Anaesthesiologists (ASA) grade I or II. (3) Weight 40–80 kg, height 140–180 cm. (4) Age 18–65 years, sex was not limited. (5) No contraindications to neuraxial anaesthesia. Exclusion criteria: (1) Patients with hypotension (SBP < 90 mmHg) or hypertension (SBP > 160 mmHg). (2) Patients' heart rate < 50 beats per minute. (3) Patients allergic to dexmedetomidine and ropivacaine. (4) Long-term use of sedatives, analgesics, adrenergic receptor antagonists and agonists. (5) Patients with lower limb motor or hearing dysfunction. (6) Liver and kidney insufficiency. Withdrawal criteria: (1) Change of anesthesia method. (2) The puncture point of epidural anesthesia was changed. (3) The patient withdrew from the experiment automatically.

Randomization and intervention

The drug formula was written on the corresponding digital card, which was sealed in an opaque envelope. Participants in each group were randomly assigned 1:1:1 to three groups according to the random number table. When participants entered the Pre anesthesia room, the nurse dispensed the medicine according to the selected card prompt. Researchers and patients were blind to the group allocation. After the trial was completed, cohorts and interventions were announced after trial termination. On the day before the operation, the anaesthesiologists explained the research process, and obtained the consent of patients and their families to sign the anesthesia informed consent and research informed consent by explaining the test process to the patient and family members.

On the day of surgery, all patients received epidural anesthesia by direct insertion method at the L_{2-3} space. After successful catheterization, 3 ml of 1.5% lidocaine (lidocaine hydrochloride injection, 5 mL:100 mg, Shiyao Yinhu Pharmaceutical Co., Ltd., China) was given to rule out the possibility of total spinal anesthesia. After 5 min, in the ED group, 15 mL 0.59% ropivacaine (Ropivacaine hydrochloride injection, 10 mL:100 mg, AstraZeneca AB, Sweden) mixed with 2 mL 0.5 μg/kg dexmedetomidine (Dexmedetomidine hydrochloride injection, 2 mL:0.2 mg, Yangtze River Pharmaceutical [Group] Co., Ltd., China) was injected to the epidural space, and the same volume of normal saline was pumped intravenously for 10 min. In the VD group, the epidural cavity was injected with 0.59% ropivacaine (15 mL) mixed with 0.9% normal saline (2 mL), and 0.9% normal saline was pumped intravenously while intravenous pumping of 0.5 μg/kg dexmedetomidine was completed within 10 min. In the NS group, 0.59% ropivacaine (15 mL) mixed with 0.9% normal saline (2 mL) was administered to the epidural space, and the same volume of normal saline was injected intravenously for 10 min. The speed of epidural injection was maintained at 0.5 mL/s, and the level of anesthesia block plane reaching T_{10} and above in bilateral pain was considered as a successful anesthesia block.

Systolic blood pressure < 90 mmHg was considered as hypotension. For the treatment of hypotension, liquid therapy should be performed firstly. If there was no improvement, 6 mg of ephedrine could be given; If the heart rate was below 50 beats per minute[14], 0.5 mg atropine was administered. Peripheral oxygen saturation (SPO_2) < 90% was considered respiratory depression and should be immediately treated with mask oxygen or respiratory support. if nausea and vomiting required medication, 4 mg ondansetron was given. Patients whose Visual Analogue Scale (VAS) score greater than 3 were given additional local anesthetics or analgesics, and the dosage of these drugs should be recorded.

Outcomes

The primary endpoint of this study was the change in SBP at T_0-$_8$. The secondary outcomes were DBP and HR at T_{0-8}, NE concentration, MVO_2 and anesthesia efficacy[15–18]. Other outcome measures include adverse reactions such as hypotension, bradycardia, nausea and vomiting, dry mouth, chills, respiratory depression, dizziness, postoperative 24-hour memory loss, as well as general information of the patients, surgical time, blood loss, infusion volume, intraoperative vasoactive drug dosage, additional local anesthetics, and analgesic drug dosage. (See supplementary materials for partial outcome indicator criteria.)

Statistical methods

The calculation of sample size was based on the results of the preliminary experiment. According to our preliminary results, the means and standard deviations of the lowest systolic blood pressure in the three groups (NS group, ED group, and VD group) were 119 (11) mmHg, 108 (11) mmHg, and 108 (12) mmHg, respectively. Assuming that $\alpha = 0.05$ and $\beta = 0.1$, 24 patients were sufficient for each group according to findings from the pilot study. A total of 90 patients were enrolled in this study ($n = 30$ in each group) to account for a potential withdrawal rate of 20%, which was calculated via PASS software. According to the distribution of the data, intergroup comparisons were conducted using One-way ANOVA, Welch test, Kruskal–Wallis H test, χ^2 test or Fisher exact probability method respectively, while intragroup comparisons were conducted using two-way repeated-measures ANOVA, Tamhane test, or Nemenyi test. Bonferroni correction was used for postevent pairwise comparisons. The P value was adjusted according to the Bonferroni method and fixed at 0.017 for pairwise comparisons. $P < 0.05$ was statistical significance.

Results

Participants and follow-up

Between June 2022 and October 2022, we screened 121 patients, 31 of whom were excluded due to not meeting the inclusion criteria. A randomized analysis of 90 patients who underwent surgery was conducted. No patients dropped out of the experiment and were lost to follow-up (Fig. 1).

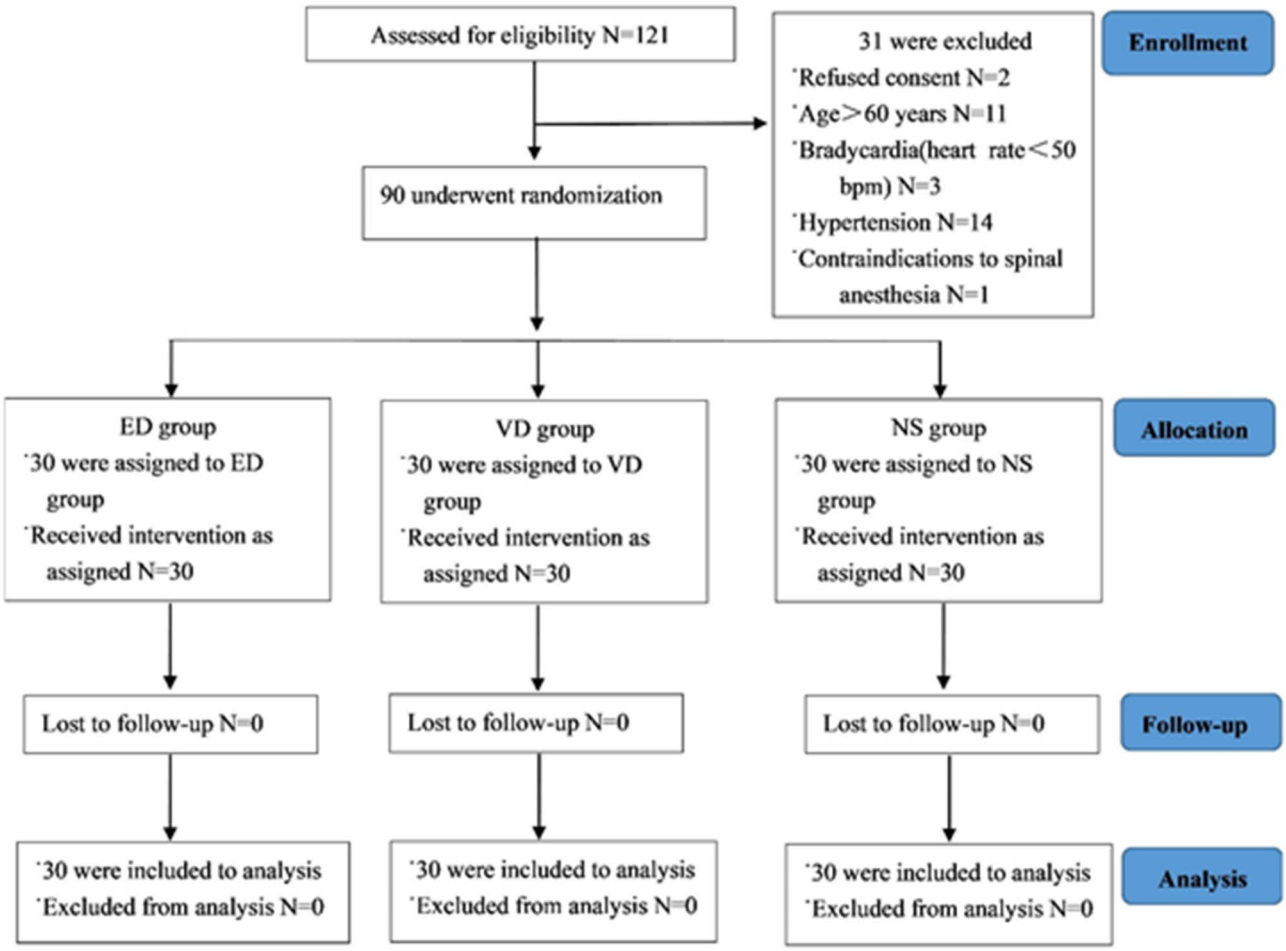

Fig. 1. CONSORT diagram. Flowchart epitomizing inclusion, allocation and analysis. ED group, epidural infusion of 0.5 μg/kg dexmedetomidine group. VD group, intravenous infusion of 0.5 μg/kg dexmedetomidine group. NS group, simple epidural infusion of the ropivacaine group.

General information of patients

There is no statistical difference in the general information and baseline characteristics of the three groups of patients ($P > 0.05$) (Table 1).

Primary and secondary outcome analysis

Haemodynamics

Compared with that in the NS group, the systolic blood pressure was lower in the ED group at T_{3-7} and lower in the VD group at T_{1-8} ($P = 0.008$, 0.001, 0.001, 0.001, 0.038 and $P < 0.001$, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.004, respectively). Compared with the VD group, the ED group had greater systolic blood pressure at T_{1-2} ($P = 0.021$ and 0.01, respectively). Compared with T_0, systolic blood pressure was significantly lower at T_{2-7} in the ED group, at T_{1-8} in the VD group, and at T_{2-5} and T_7 in the NS group ($P = 0.003$, 0.001, 0.001, 0.001, 0.001, 0.023 and all $P < 0.001$ and $P < 0.001$, 0.001, 0.003, 0.015, 0.047, respectively) (Fig. 2A).

Compared with the NS group, the ED group had lower diastolic blood pressure at T_{4-5} and T_7, and the VD group had lower diastolic blood pressure at T_{1-8} ($P = 0.017$, 0.006 0.044 and $P < 0.001$, 0.001, 0.001, 0.002, 0.001, 0.001, 0.001, 0.036, respectively). Compared with that in the VD group, diastolic blood pressure was greater in the ED group at T_{1-2} ($P = 0.001$, 0.011, respectively). Compared with T_0, diastolic blood pressure was significantly lower at T_{3-5} in the ED group and at T_{1-8} in the VD group ($P = 0.024$, < 0.001, < 0.008 and all $P < 0.001$, respectively), and there was no significant difference in diastolic blood pressure at any time point in the NS group ($P > 0.05$) (Fig. 2B).

Compared with the NS group, the ED group presented a significant reduction in heart rate at T_{3-4} and T_{6-7} ($P < 0.001$, 0.021, 0.002, 0.004, respectively), whereas the VD group presented no significant difference in heart rate at any time point ($P > 0.05$). Compared with the VD group, the ED group had a significantly lower heart rate at T_7 ($P < 0.001$). Heart rates were significantly lower at T_{1-8} in the ED group, at T_{1-8} in the VD group, and at T_{3-5} in the NS group than at T_0 ($P = 0.001$, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.017 and $P < 0.001$, 0.001, 0.001, 0.001, 0.001, 0.001, 0.004, 0.049 and $P = 0.002$, 0.001, 0.001, respectively) (Fig. 2C).

Compared with those in the NS group, the NE concentrations were significantly lower in the VD group at T_{3-7} and in the ED group at $T_{3-4,\,6-7}$ (all $P < 0.001$ and $P = 0.002$, 0.001, 0.001, 0.001, respectively). Compared with the VD group, the ED group presented significantly greater NE concentrations at T_{3-6} (all $P < 0.001$). Compared with those at T_0, NE concentrations were significantly lower at T_{3-5} in the VD group and were greater in the NS group at T_4 ($P = 0.009$, 0.001, 0.001 and $P = 0.005$, respectively), and there was no significant difference in NE concentrations at any time point in the ED group ($P > 0.05$) (Fig. 3A).

Compared with that in the NS group, myocardial oxygen consumption was significantly lower in the ED group at T_{3-8} and in the VD group at T_{1-6} ($P < 0.001$, 0.001, 0.001, 0.001, 0.001, 0.035 and all $P < 0.001$, respectively). Compared with the VD group, the ED group presented a significant decrease in myocardial oxygen consumption at T_{1-2} ($P = 0.009$ and 0.05, respectively). Compared with T_0, myocardial oxygen consumption was significantly lower at T_{2-8} in the ED group, at T_{1-8} in the VD group, and at T_{2-5} and T_7 in the NS group ($P < 0.001$, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001 and all $P < 0.001$ and $P = 0.002$, 0.001, 0.001, 0.001, 0.005, respectively) (Fig. 3B).

Anaesthetic effects

Compared with the NS group, the ED group had significantly lower VAS scores at T_{6-8} (all $P < 0.001$), and the VD group had significantly lower VAS scores at T_6 ($P = 0.038$). Compared with that in the VD group, the VAS score in the ED group at T_{7-8} was significantly lower (all $P < 0.001$) (Fig. 4A).

Compared with that of the NS group, the Ramsay score was significantly increased at T_{2-5} in the ED group and at T_{1-5} in the VD group (all $P < 0.001$). Compared with the VD group, the ED group had significantly lower Ramsay scores at T_{1-2} ($P < 0.001$, 0.031, respectively) (Fig. 4B).

Compared with the NS and VD groups, the ED group had a greater maximum block plane ($P = 0.012$) and motor block score ($P < 0.001$), a faster onset of anaesthesia ($P < 0.001$), a longer time to analgesia ($P < 0.001$), a longer recovery of lower limb muscle strength ($P < 0.001$), and a longer time to fall asleep ($P < 0.001$). No

	NS group ($n = 30$)	VD group ($n = 30$)	ED group ($n = 30$)	F/H/χ^2	*P*-value
Age (year)	58.5 (8.5)	58.5 (17.0)	56.5 (7.8)	2.029	0.363
Gender (male/female)	17/13	14/16	18/12	1.165	0.559
ASA (I/II)	16/14	17/13	14/16	0.800	0.670
Body weight (kg)	65.3 (8.2)	64.5 (9.7)	66.1 (9.4)	0.223	0.800
Height (cm)	161.1 (7.2)	164.4 (7.8)	164.6 (8.3)	2.499	0.088
Operation time (min)	113.6 (42.4)	110.1 (32.3)	115.3 (42.9)	0.135	0.874
Infusion volume (ml)	1056.7 (280.0)	1098.3 (207.8)	1050.0 (289.8)	0.300	0.741
blood loss (ml)	100.0 (70.0)	80.0 (32.5)	80.0 (20.0)	2.477	0.290
Use of vasoactive drug (yes/no)	2/28	4/26	2/28	1.057	0.722
Use of antiemetic (yes/no)	0/30	0/30	0/30	0.000	1.000
Additional local anaesthetics and analgesic drugs (yes/no)	0/30	0/30	0/30	0.000	1.000

Table 1. General data comparison between the three groups (mean (SD), median (IQR), relative numbers (R)).

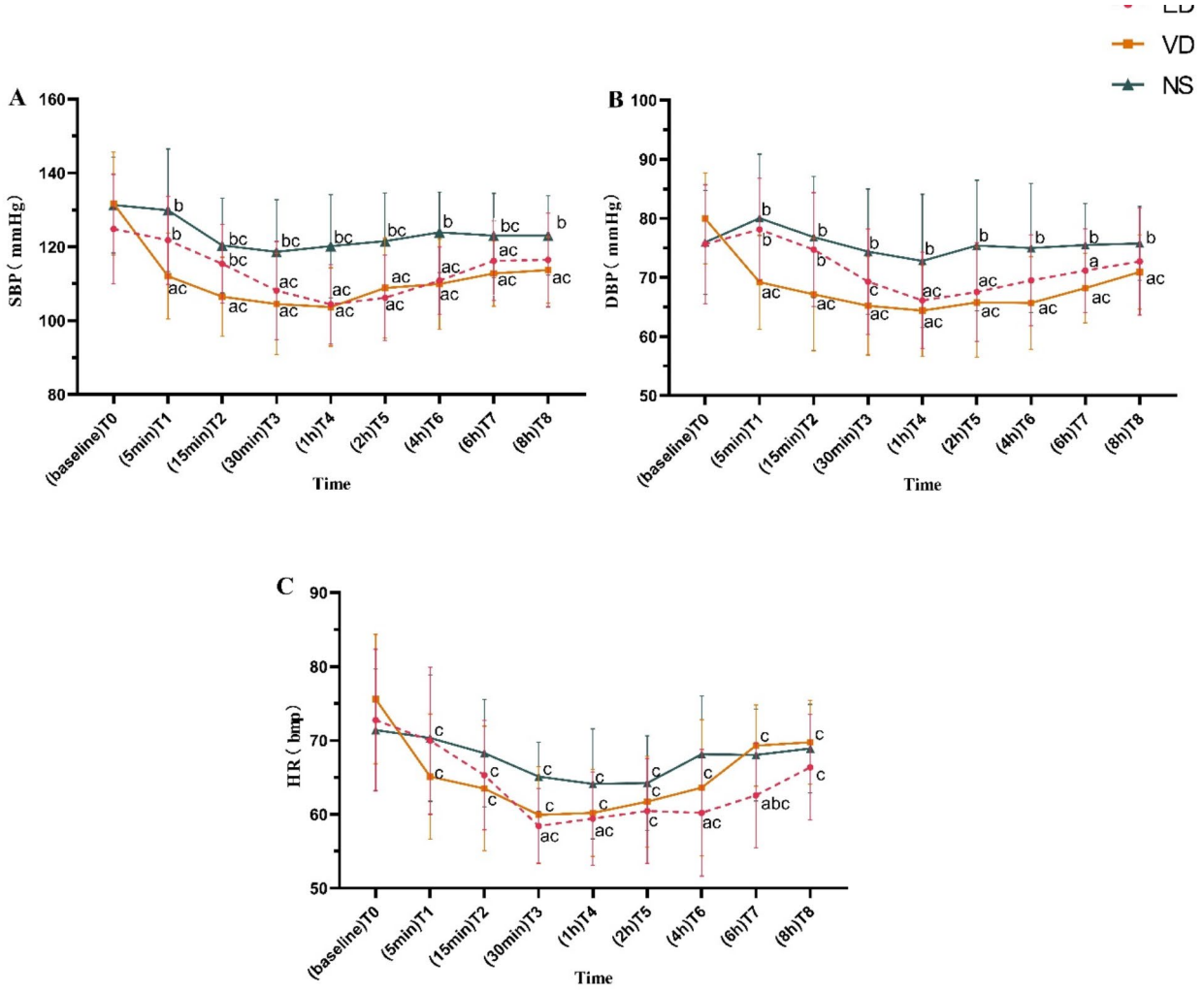

Fig. 2. (**A**) Systolic blood pressure of ED group, VD group and NS group at baseline and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after administration. (**B**) Diastolic blood pressure of ED group, VD group and NS group at baseline and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after administration. (**C**) Heart rate of ED group, VD group and NS group at baseline and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after administration. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate. NS group, ropivacaine plus isovolumic saline epidural infusion group; VD group, dexmedetomidine intravenous infusion combined with ropivacaine epidural infusion group; ED group, dexmedetomidine combined with ropivacaine epidural infusion group. [a]$P<0.05$, vs. NS group; [b]$P<0.05$, vs. VD group; [c]$P<0.05$, vs. T_0, both comparisons were corrected by Bonferroni.

significant alterations in anaesthesia efficacy were identified in the VD group compared with the NS group ($P>0.05$) (Table 2).

Adverse reactions

Compared with that in the NS group, the incidence of dizziness was significantly greater in the ED group ($P=0.008$), and the incidence of hypotension and dizziness in the VD group was significantly greater ($P=0.02$, 0.016, respectively). Hypotension was less common in the ED group than in the VD group ($P=0.002$) (Table 3).

Discussion

The results of our study revealed that epidural or intravenous infusions of dexmedetomidine could suppress the perioperative haemodynamics of patients to varying degrees compared with those of the control group in patients who underwent saphenectomy with epidural anaesthesia. In addition, compared with the VD group, the ED group had better haemodynamics, a lower incidence of hypotension, a shorter onset of anaesthesia, more comprehensive blockade, and longer analgesia.

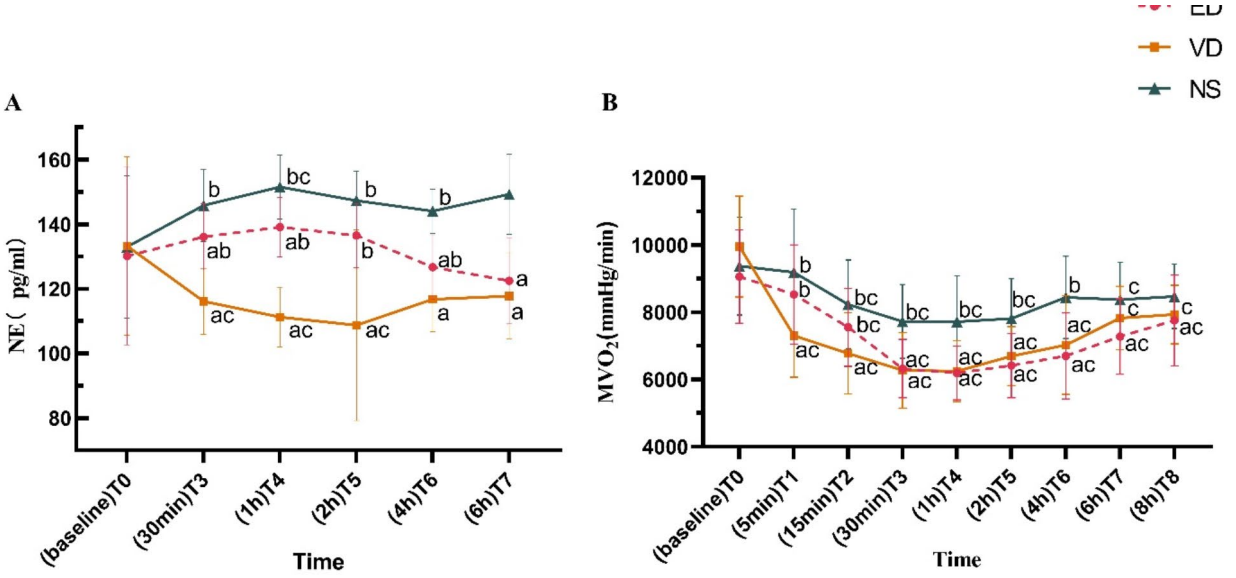

Fig. 3. (**A**) Norepinephrine of ED group, VD group and NS group at baseline and at 30 min, 1 h, 2 h, 4 h and 6 h after administration. (**B**) Myocardial oxygen consumption of ED group, VD group and NS group at baseline and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 8 h after administration. NE norepinephrine, MVO_2 myocardial oxygen consumption. NS group, ropivacaine plus isovolumic saline epidural infusion group; VD group, dexmedetomidine intravenous infusion combined with ropivacaine epidural infusion group; ED group, dexmedetomidine combined with ropivacaine epidural infusion group. [a]$P<0.05$, vs. NS group; [b]$P<0.05$, vs. VD group; [c]$P<0.05$, vs. T_0, both comparisons were corrected by Bonferroni.

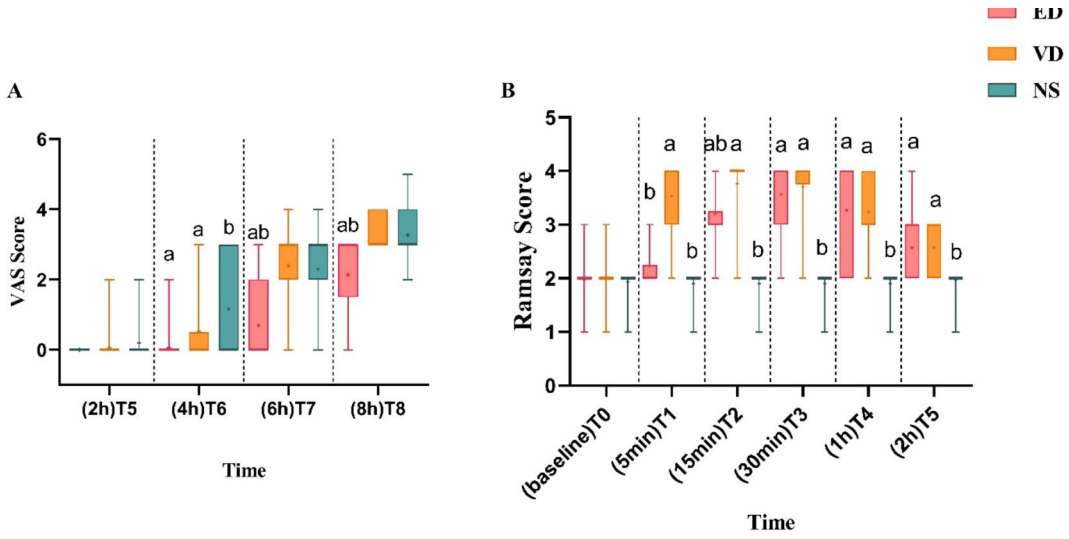

Fig. 4. (**A**) ED group, VD group, and NS group were scored with VAS scores at 2 h, 4 h, 6 h, and 8 h after administration. (**B**) ED group, VD group, and NS group were scored with Ramsay scores at baseline and at 5 min, 15 min, 30 min, 1 h and 2 h after administration. VAS visual analogue scale. NS group, ropivacaine plus isovolumic saline epidural infusion group; VD group, dexmedetomidine intravenous infusion combined with ropivacaine epidural infusion group; ED group, dexmedetomidine combined with ropivacaine epidural infusion group. [a]$P<0.05$, vs. NS group; [b]$P<0.05$, vs. VD group, boxes indicate the median with the 25th and 75th percentiles (interquartile range), whisker caps represent the minimum and maximum values, and + represents the average.

	NS group ($n=30$)	VD group ($n=30$)	ED group ($n=30$)	F/H	*P*
Maximum sensory block level $T_6/T_8/T_{10}$	8/21/1	9/20/1	18/12/0[ab]	8.832	0.012
Motor block score <2 score/2–4score/>4score	0/2/28	0/8/22	0/26/4[ab]	42.852	<0.001
Onset time of sensory block at T_{10} (min)	14.0 (5.0)	12.0 (3.3)	8.0 (1.0)[ab]	52.291	<0.001
Time to fall asleep (min)	–	15.0 (3.5)	25.0 (10.0)[b]	100.500	<0.001
Time of analgesia (min)	268.1 (87.7)	278.4 (54.4)	392.9 (59.2)[ab]	36.351	<0.001
Recovery time of lower limb muscle strength (min)	249.0 (54.9)	252.1 (74.5)	327.8 (58.7)[ab]	14.392	<0.001
Patient satisfaction with anaesthesia	6.0 (2.0)	7.0 (1.3)[a]	8.0 (2.3)[a]	19.656	<0.001

Table 2. Comparison of anaesthesia effects among the three groups (mean (SD), median (IQR), relative numbers (R)). [a]$P<0.05$, vs. NS group. [b]$P<0.05$, vs. VD group; both comparisons were corrected by Bonferroni.

	NS group ($n=30$)	VD group ($n=30$)	ED group ($n=30$)	χ^2	*P*
Hypotension	4 (13.3)	12 (40)	2 (6.7)[b]	11.667	0.003
Bradycardia	1 (3.3)	2 (6.7)	5 (16.7)	3.108	0.263
Dizziness	0 (0)	7 (23.3)[a]	8 (26.7)[a]	9.120	0.010
Nausea and vomiting	0 (0)	0 (0)	1 (3.3)	2.022	0.364
Dry mouth	0 (0)	4 (13.3)	2 (6.7)	4.086	0.159
Chills	0 (0)	0 (0)	0 (0)	0.000	1.000
Respiratory depression	0 (0)	0 (0)	0 (0)	0.000	1.000
24-h postoperative amnesia	0 (0)	0 (0)	0 (0)	0.000	1.000
Vasoactive drug use	2 (6.7)	4 (13.30	2 (6.7)	1.098	0.578

Table 3. Comparison of intraoperative and postoperative adverse events between the three groups (n_1(%)). n_1, Number of cases of each adverse reaction. [a]$P < 0.05$, vs. NS group. [b]$P < 0.05$, vs. VD group; both comparisons were corrected by Bonferroni.

Intravenous or epidural infusion of dexmedetomidine for the management of perioperative patients has been proven to be beneficial and valid in many studies. The influence of dexmedetomidine on haemodynamics also cannot be ignored. Previous studies[19,20] have shown that dexmedetomidine can inhibit perioperative haemodynamics in patients to a certain extent, which is consistent with the results of the present study.

Compared with that in the control group, the blood pressure in the intravenous group began to decrease significantly 5 min after the infusion of dexmedetomidine and 15 min after the infusion of dexmedetomidine in the epidural group. Although the standard of hypotension in our experiment was a systolic blood pressure < 90 mmHg, in the intravenous group, the systolic blood pressure decreased by more than 20% of the base value after 30 min and after 1 h of infusion of dexmedetomidine (20.7% and 21.3%, respectively), whereas the decrease in systolic blood pressure in the epidural group did not exceed 20% of the basal value (Fig. 2A). In this study, compared with intravenous infusion, 0.5 μg/kg dexmedetomidine had a weaker effect on blood pressure at 5 min and 15 min after the completion of epidural infusion (Fig. 2A and B) and resulted in lower heart rate at 6 h after epidural infusion (Fig. 2C). Overall, the decrease in haemodynamics in the epidural group was more moderate, with fewer episodes of hypotension.

These findings may be supported by the evaluation of the pharmacokinetics and pharmacodynamics of dexmedetomidine. After intravenous infusion of dexmedetomidine, the maximum concentration is reached in the blood in approximately 2 min, with a distribution half-life of approximately 6 min and an elimination half-life of approximately 2–3 h. Highly fat-soluble dexmedetomidine easily crosses the blood-brain barrier, can be rapidly distributed peripherally to the centre, inhibits the sympathetic nervous system, and enhances the activity of the vagus nerve, resulting in decreased blood pressure and heart rate[21]. In addition, systemic administration of dexmedetomidine can also induce central hypotension as well as heart rate slowing by binding to imidazoline receptor 1 [22,23].

After epidural administration of dexmedetomidine in ewes, it is rapidly detected in the cerebrospinal fluid, reaching its maximum concentration within 5 min, with a distribution half-life equivalent to 0.7 min and elimination half-life of 25 min, and approximately 22% of the total dose is absorbed into the subarachnoid space[24,25]. Dexmedetomidine, on the other hand, can easily enter the spinal cord and brain after administration via the epidural route, act on the rostral ventrolateral medulla (cardiovascular regulatory centre, RVLM), downregulate the neuronal activity of the RVLM[26], and, in turn, cause a decrease in vascular resistance.

Differences between systemic or epidural administration are also related, to some extent, to differences in lipid solubility and meningeal penetration[26]. Dexmedetomidine, when administered via the epidural route, can be absorbed at multiple sites, such as by acting on spinal nerve roots and entering the brain through cerebrospinal fluid and blood, and the amount of dexmedetomidine bound to spinal cord α_2 adrenoreceptors is

significantly greater than that in the brain[26]. Therefore, a possible explanation may be that, owing to the different administration routes, the starting time and concentration of dexmedetomidine affected the cardiovascular regulatory centre differently, and ultimately, the blood pressure and heart rate tended to decrease more gradually in the epidural group than in the intravenous group. Nevertheless, this discrepancy in the above results should be interpreted with caution, given that our trial was underpowered to derive any definite explanation regarding this phenomenon.

In addition, the ED group appeared to have a greater effect on patients' heart rate than the VD group did, suggesting that the epidural infusion of dexmedetomidine had a greater effect on heart rate than on blood pressure in patients undergoing saphenectomy. This may be due to the additive effect of epidural infusion of dexmedetomidine on cardiac sympathetic vagal nerve activity through multiple pathways, so patients who undergo saphenectomy with sinus bradycardia should be careful in choosing an epidural infusion of dexmedetomidine.

In the present study, plasma NE concentrations were lower in the VD and ED groups than in the NS group, which was considered to reflect the pharmacological effect of dexmedetomidine in inhibiting the central sympathetic nervous system and thus inhibiting peripheral NE release. At 30 min, 1 h, and 2 h after drug administration, a significant decline in the plasma NE concentration was observed in the VD group compared with the ED and NS groups, which was in line with the above trend of blood pressure changes in the three groups, indicating that dexmedetomidine principally reduces peripheral vascular resistance by decreasing NE release, resulting in dilated blood pressure reduction[27]. Notably, both epidural and intravenous dexmedetomidine effectively decreased myocardial oxygen consumption in perioperative patients. This phenomenon might be explained by the trend and mechanism of blood pressure and heart rate changes in both groups. A reduction in myocardial oxygen consumption can alleviate cardiac burden and decrease cardiac accidents, which is especially beneficial in patients with cardiac diseases such as coronary heart disease.

An increasing body of data suggests that epidural infusion of dexmedetomidine significantly enhances the efficacy of epidural anaesthesia[10,28,29], which is identical to the secondary endpoint of our trial. In this study, we found that 0.5 μg/kg dexmedetomidine as an adjunct to epidural ropivacaine (ED group) markedly shortened the onset time of anaesthesia, improved the highest plane of the block, and prolonged the analgesia time compared with those in the VD and NS groups. The antinociceptive effects of dexmedetomidine were graded as intrathecal > epidural ≥ intravenous[30]. Epidural α_2 agonists are approximately five times more effective than systemic administration in producing antinociceptive effects[26], suggesting that the antinociceptive effect of epidural infusion of dexmedetomidine is considered to be much greater than the vasodilatory effect.

Under epidural anesthesia, as the patients are in a conscious state, they are prone to nervous anxiety, leading to increased sympathetic nervous activity and ultimately resulting in increased myocardial oxygen consumption. This inarguably reduces the quality of recovery and results in a worse patient experience. Dexmedetomidine, as an anaesthetic adjunct, provides excellent sedation by acting on α_2 receptors in the central Locus Coeruleus region, which has been confirmed in previous studies[31,32]. Consistent with this experiment, sedation scores in the VD and ED groups reached approximately 3–4 points at 15 min, 30 min, 1 h, and 2 h after drug administration. Compared with that in the NS group, the sedative effect of dexmedetomidine significantly improved the anaesthesia satisfaction of patients in the VD group and ED group.

With respect to adverse event outcomes, the incidence of hypotension in the 3 groups was approximately 13.33% in the NS group, approximately 40% in the VD group, and approximately 6.67% in the ED group, indicating that dexmedetomidine epidural infusion was more stable in terms of haemodynamics than intravenous infusion in patients undergoing saphenectomy. A small percentage of patients in the VD and ED groups presented with bradycardia, dry mouth, and dizziness symptoms. Moreover, we should be cautious in choosing dexmedetomidine for patients with low sympathetic activity, such as bradycardia or hypotension.

Limitations

(1) In this study, surgery involving large haemodynamic fluctuations was not selected because the benefits of dexmedetomidine are more easily manifested during major surgery. However, since there are too many uncontrollable factors in major surgery, interference easily occurs. Saphenous vein decortication requires low muscle relaxation and relatively little blood loss, which can improve our results. In the future, further experiments can be carried out in major surgery populations. (2) Although this study verified that 0.5 μg/kg dexmedetomidine epidural infusion has a weaker effect on the patient's perioperative circulation than does intravenous infusion and exerts a good anaesthetic effect, it remains uncertain whether the recommended dose of epidural infusion of dexmedetomidine can not only ensure haemodynamic stability but also achieve the best anaesthesia effect with few adverse reactions, which needs to be further investigated. (3) In this study, although the heart rate of the intravenous infusion group was reduced to varying degrees compared with that of the control group at various time points, there was no clinically significant difference between the two groups, possibly because the sample size was calculated according to the primary outcomes, which may not be sufficient for these secondary outcomes. Therefore, a larger, multicentre, and sufficiently powered trial is needed to definitively assess the results.

Conclusion

In patients undergoing saphenectomy with epidural anaesthesia, 0.5 μg/kg dexmedetomidine epidural infusion has more stable haemodynamics than intravenous infusion does, a lower incidence of hypotension, more complete blockade, better anaesthetic effects, and a shorter onset time of anaesthesia, which is conducive to improving patient satisfaction with anaesthesia and optimizing perianaesthetic management. However, for patients with low sympathetic activity, such as bradycardia or hypotension, we should be cautious about the use of dexmedetomidine.

Data availability

All data generated or analysed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and informed consent
All procedures performed on the patients were in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments. This protocol was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Ref. 2022ER073-1). Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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