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Effects of pre-injection of pressors on pressor response and bispectral index of patients receiving lower abdominal surgery under total intravenous anesthesia

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Surgery in the lower abdomen can cause many adverse reactions in nervous system, metabolic and endocrine systems. Conventional intravenous anesthesia applied for lower abdominal surgery can cause the drop in blood pressure leading to hypoperfusion of vital organs. Hence, an ideal anesthesia state is required to make patients unconscious, unaware and have no postoperative memory during anesthesia. In this study, we investigated the effects of pre-injection of different pressors on the pressor response and bispectral index (BIS) of patients receiving lower abdominal surgery under total intravenous anesthesia. For this, 300 patients undergoing lower abdominal surgery under total intravenous anesthesia in the Jinhua Hospital, Zhejiang, were divided into normal saline (Gr. A), ephedrine (Gr. B) and phenylephrine groups (Gr. C) (n=100). Hemodynamics indices were recorded before anesthesia induction (T0) and 1, 3, 5, 7 and 9 min after drug injection (T1-T5, respectively). We observed the following reactions and recorded. BIS values at T0-T5 as well as the time points when the values rose to 65, 75, 85 and 95 and those for respiratory recovery, consciousness recovery and extubation after stopping target-controlled infusion were recorded. Compared with Gr. A, Gr. B had significantly higher systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and cardiac output (CO) at T1-T5 (P <0.05), and Gr. C had higher SBP, DBP, MAP and lower HR (P <0.05). Adverse reactions *viz*., intraoperative hypotension, hypertension, postoperative bradycardia, tachycardia, nausea and vomiting were also observed. The incidence rates of hypotension and total adverse reactions in groups B and C were significantly lower than those of Gr. A (P <0.05). Group B had significantly higher BIS values at T1-T5 than those of Gr. A (P <0.05). The time when BIS values recovered to 65 and 75 in group B was significantly shorter than that of Gr. A (P <0.05). Pre-injection of ephedrine and phenylephrine to patients undergoing lower abdominal surgery under total intravenous anesthesia elevated the blood pressure and reduced the incidence rate of adverse reactions without affecting the recovery time.

Keywords: Ephedrine, Phenylephrine

Lower abdominal surgery leads to a series of stress reactions, including changes in nervous, metabolic and endocrine systems. To achieve an ideal anesthesia state, it is necessary to make patients unconscious, unaware and have no postoperative memory during anesthesia. Besides, the fluctuation of blood pressure and heart rate to noxious stimulation should not exceed 30% of the baseline value, and patients should be satisfactory after surgery. At present, conventional intravenous anesthesia is mostly applied for lower abdominal surgery, but it easily causes the drop of blood pressure during anesthesia, resulting in the hypoperfusion of vital organs and even cardiovascular and cerebrovascular accidents in severe cases[1]. Additionally, intraoperative endotracheal intubation is also a key factor resulting in stress reaction as well as blood pressure and heart rate fluctuations[2]. Therefore, preventing and treating intraoperative hypotension are of great significance to the safety of patients.

Vasoactive drugs mainly affect blood pressure by regulating the tension of vascular smooth muscle and the function of cardiac pump. The drugs commonly used to correct hypotension primarily include vasoconstrictors and drugs enhancing myocardial contractility, and they work mainly at epinephrine α1-receptor and β1-receptor. At present, vasopressors that are commonly applied in clinical practice to correct hypotension mainly include ephedrine, phenylephrine, dopamine and epinephrine. Ephedrine and phenylephrine are usually injected intravenously at single doses to quickly correct hypotension. Ephedrine is able to directly excite epinephrine receptor or indirectly excite it by facilitating the release of norepinephrine from adrenergic nerve endings. In addition, ephedrine can excite both α- and β-epinephrine receptors, with similar pharmacological effects to those of epinephrine[3,4]. Nevertheless, the

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effects of pre-injection of ephedrine or phenylephrine before total intravenous anesthesia on the pressor response of patients undergoing lower abdominal surgery remain elusive. Here, we studied the impact of pre-injection of pressors (ephedrine and phenylephrine) on patients undergoing lower abdominal surgery under total introvenous anesthesia.

Subjects and Methods

Baseline clinical data

This study has been approved by the ethics committee of Jinhua Hospital from 2017 to 2020, and written informed consents were obtained from all patients who had participated in this study. Three hundred patients undergoing lower abdominal surgery in our hospital were selected, including 185 males and 115 females aged 24-65 years old, with an average of (46.81 ± 9.82) and a body mass index (BMI) of (20.65 ± 1.24) kg/m^2. The surgical methods included appendectomy (n=92), hysterectomy or adnexal hysterectomy (n=85), rectal tumor resection (n=51), bladder tumor resection (n=39), adrenalectomy and renal tumor resection (n=24), and others (n=9). Then these patients were divided into a normal saline group (Gr. A), an ephedrine group (Gr. B) and a phenylephrine group (Gr. C), each with n=100. Inclusion criteria: (i) Patients who planned to receive lower abdominal surgery; (ii) those who were in Grade I-II classified by the American Society of Anesthesiologists (ASA). Exclusion criteria: (i) Patients who were allergic to anesthetics; (ii) those with history of serious cardiovascular and cerebrovascular diseases; (iii) those with mental disorders or related history; (iv) those with postoperative massive hemorrhage or anaphylactic shock; and (v) those with incomplete medical data.

Methods

Patients were fasted for 6 h before surgery. After they entered the operating room, an 18 G indwelling needle was used to establish a pathway in the upper limb vein, via which 6 mL/kg sodium lactate Ringer′s solution (Otsuka Pharmaceutical Co., Ltd., China; batch No. 7G69A9) was intravenously infused. Blood pressure, heart rate (HR) and bispectral index (BIS) were measured every 2 min after 10 min of rest. The values obtained at 3 time points were averaged as the values before anesthesia induction (T0). Afterwards, Groups A-C were injected with normal saline (Otsuka Pharmaceutical Co., Ltd., China; batch No. 17102241), 1 μg/kg ephedrine (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; batch No. 20180613) and 1.5 μg/kg phenylephrine (Shanghai Harvest Pharmaceutical Co., Ltd., China; batch No. 07180523), respectively. All patients underwent endotracheal intubation and total intravenous anesthesia as follows:(i) Anesthesia induction: Briefly, 0.05 mg/kg midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., China; batch No. 20180202), 1-2 mg/kg propofol (Guangdong Jiabo Pharmaceutical Co., Ltd., China; batch No. 2A180903-6), 0.5 μg/kg fentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., China; batch No. 6180081) and 0.15 mg/kg cisatracurium (Jiangsu Hengrui Medicine Co., Ltd., China; batch No. 180621AK) were injected intravenously sequentially. Following the loss of consciousness, the patients received endotracheal intubation, and connected to an anesthesia machine; (ii) Anesthesia maintenance: Patients were intravenously injected continuously with 4-8 mg/(kg·h) propofol and 0.2 μg/(kg·h) remifentanil through a pump, and intermittently with cisatracurium; and (iii) Anesthesia termination: The injection of cisatracurium was stopped 10 min before the end of surgery, and the pumping of propofol and sufentanil was terminated finally.

Surgical indices

The surgical time, anesthesia time, propofol dose, intraoperative infusion volume, intraoperative urine volume, blood loss volume, autologous blood recovery volume, together with hemoglobin (Hb) level and hematocrit (Hct) before and 1 d after surgery were recorded.

Hemodynamics indices

Hemodynamics indices, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), systemic vascular resistance (SVR) and stroke volume variation (SVV), were recorded before anesthesia induction (T0), and 1, 3, 5, 7 and 9 min after drug injection (T1-T5, respectively).

Adverse reactions

Adverse reactions, such as intraoperative hypotension (SBP: <80 mmHg or reduction by over 20% of the baseline value), hypertension (SBP: elevation by over 20% of the baseline value), postoperative bradycardia (HR: <60 bpm), tachycardia (HR: >100 bpm), nausea and vomiting, were also recorded.

Monitoring of BIS

BIS values at T0-T5 were detected by Aspect Bis A-2000 BIS monitor (USA).

Recovery time

The time points when BIS values rose to 65, 75, 85 and 95 after stopping target-controlled infusion, as well as those for respiratory recovery (spontaneous breathing frequency exceeded 6 times/min), consciousness recovery (ability to complete required movements such as blinking and nodding) and extubation (spontaneous breathing frequency exceeded 12 times/min, tidal volume was over 300 mL, and hemodynamic indices remained stable) were recorded.

Statistical analysis

All data were statistically analyzed by SPSS 19.0 software. The quantitative data were expressed as mean ± standard deviation, and the numerical data were represented as frequency or rate. Intergroup comparisons were performed by the independent samples t test and χ^2 test. Two-tailed P <0.05 was considered statistically significant.

Results

Baseline clinical data and surgical indices

The three groups had similar age, gender ratio, body weight, BMI and ASA grade (Table 1). There were no significant differences between the surgical time, anesthesia time, propofol dose, intraoperative infusion volume, intraoperative urine output, blood loss, autologous blood recovery volume, or preoperative and postoperative Hb levels and Hct of the three groups (Table 2).

Hemodynamics indices

At T0, the three groups had similar hemodynamics indices. Compared with T0, SBP and DBP of Gr. A significantly decreased at T1-T5, MAP significantly reduced at T1-T3, HR decreased at T1 and increased at T2-T5, CO hardly changed at T1-T5, SVR rose significantly at T1-T2, and SVV dropped significantly at T1-T3 (P <0.05). In Gr. B, SBP increased significantly at T1-T4, DBP, MAP, HR and CO rose significantly at T1-T5, SVR increased significantly at T1-T2, and SVV decreased at T2-T5 (P <0.05). In Gr. C, SBP increased significantly at T1-T3, DBP rose significantly at T1-T5, MAP increased significantly at T1-T4, HR decreased significantly at T1-T5, CO increased at T4-T5, SVR rose significantly at T1-T4, and SVV decreased significantly at T1-T5 (P <0.05).

Table 1 — Baseline clinical data

Index	Groups (n=100)			F/χ^2 value	P value
	A	B	C		
Age (year)	46.21±8.12	45.97±8.35	46.57±9.01	1.396	0.537
Gender [male/female (case)]	62/38	64/36	59/41	0.536	0.765
Body weight (kg)	63.12±7.52	62.85±7.28	63.53±7.73	0.934	0.210
BMI (kg/m^2)	24.47±2.32	23.78±2.08	24.52±2.15	1.223	0.322
ASA grade I/II (case)	79/21	68/32	74/26	3.127	0.209

[Groups A, B and C: normal saline, ephedrine and phenylephrine, respectively]

Table 2 — Hemodynamics indices ($\bar{x} \pm s$)

Index	Groups	T0	T1	T2	T3	T4	T5
SBP (mmHg)	A	124.2±11.3	96.4±8.6*	108.5±10.8*	98.3±9.8*	95.7±8.9*	90.2±8.4*
	B	124.1±10.7	128.7±12.1*#	135.4±13.5*#	132.4±12.8*#	129.4±12.5*#	126.5±12.9#
	C	123.6±10.2	126.9±12.6*#	131.3±11.4*#	129.2±10.6*#	125.8±10.9#	124.3±11.1#
DBP (mmHg)	A	76.3±7.8	58.3±7.1*	65.4±6.8*	63.9±7.0*	59.5±6.6*	54.7±6.5*
	B	75.8±7.2	95.8±8.3*#	102.4±10.4*#	97.2±10.1*#	95.2±9.5*#	92.2±8.7*#
	C	76.0±7.4	93.8±8.0*#	97.5±9.4*#	95.2±9.1*#	93.6±9.0*#	89.3±8.5*#
MAP (mmHg)	A	62.6±6.9	55.8±6.2*	58.6±6.9*	60.5±6.4*	61.3±6.9	60.6±6.7
	B	62.4±7.2	78.5±7.2*#	83.6±7.2*#	79.1±7.0*#	72.7±7.1*#	70.3±7.0*#
	C	63.2±7.0	77.3±7.0*#	81.4±7.1*#	73.1±7.2*#	72.7±6.9*#	64.3±6.8#
HR (bpm)	A	83.2±7.5	78.5±7.2*	86.6±7.3*	89.1±7.4*	88.7±7.1*	85.3±7.0*
	B	83.8±7.4	94.5±8.2*#	94.3±8.3*#	94.7±8.2*#	91.2±7.9*#	89.3±7.6*#
	C	84.3±7.1	74.5±7.2*#	75.3±8.5*#	72.7±8.2*#	69.7±7.0*#	68.3±7.2*#
CO (L/min)	A	3.7±0.7	3.9±0.8*	3.8±0.5	3.8±0.6	3.8±0.5	3.8±0.4
	B	3.8±0.8	4.6±0.8*#	4.3±0.6*#	4.3±0.5*#	4.3±0.7*#	4.3±0.5*#
	C	3.7±0.6	3.8±0.5	3.8±0.6	3.8±0.5	3.9±0.7*	3.9±0.5*
SVR ($dyn \cdot s \cdot cm^{-5}$)	A	1346.1±304.5	1472.5±273.4*	1453.6±253.4*	1414.1±249.8	1374.1±249.8	1356.8±237.5
	B	1351.2±298.2	1579.3±278.3*#	1473.1±286.1*	1420.6±256.8	1384.7±249.3	1367.7±248.2
	C	1342.7±301.3	1739.4±326.1*#	1628.1±301.2*#	1574.1±283.4*#	1421.1±262.5	1384.1±257.8
SVV (%)	A	9.8±2.5	8.6±2.0*	8.4±2.3*	8.9±2.1*	9.2±2.2	9.4±2.6
	B	9.2±2.1	8.8±3.0	7.1±2.2*#	7.2±2.4*#	7.0±2.3*#	8.0±2.5*#
	C	9.5±2.0	8.7±2.1*	8.5±2.2*	8.4±2.3*	8.6±2.1*	8.7±2.2*

[Groups A, B and C: normal saline, ephedrine and phenylephrine, respectively. Level of significance: Compared with T0, *P <0.05; compared with Gr. A, #P <0.05]

Compared with Gr. A, SBP, DBP, MAP, HR and CO of Gr. B significantly increased at T1-T5, SVR significantly rose at T1, and SVV significantly decreased at T2-T4 (P <0.05). SBP, DBP, and MAP of Gr. C were significantly higher than those of Gr. A at T1-T5, and HR was significantly lower at T1-T5. There was no significant change in CO. SVR was significantly higher at T1-T3 than that of Gr. A, and SVV was significantly higher at T1 and lower at T2-T5 (P <0.05) (Table 2). Collectively, both groups B and C underwent significant increase of blood pressure. Group B had longer working time, accompanied by HR, CO increase and SVV decrease. Group C was subjected to HR reduction and SVR elevation.

Adverse reactions

The incidence rates of hypotension and total adverse reactions in groups B and C were significantly lower than those of Group A (P <0.05) (Table 3).

BIS values

The three groups had similar BIS values at T0. Group B had significantly higher BIS values at T1-T5 than those of Gr. A (P <0.05), but the values of groups C and A were similar (Table 4).

BIS recovery and anesthesia recovery times

The time when BIS values recovered to 65 and 75 in group B was significantly shorter than that of Gr. A (P <0.05), but the two groups had similar times when BIS values recovered to 85 and 95 and for respiratory recovery, consciousness recovery and extubation (P >0.05). There were no significant differences between groups C and A (P >0.05) (Table 5).

Table 3 — Adverse reactions [case (%)

Index	Groups (n=100)			χ^2 value	P value
	A	B	C		
Intraoperative hypotension	21 (21)	1 (1)$^{\#}$	3 (3)$^{\#}$	31.77	0.000
Intraoperative hypertension	0 (0)	3 (3)	1 (1)	3.55	0.170
Postoperative bradycardia	2 (2)	0 (0)	4 (4)	4.08	0.130
Postoperative tachycardia	2 (2)	5 (5)	0 (0)	5.56	0.062
Nausea and vomiting	3 (3)	2 (2)	1 (1)	1.02	0.600
Total	28 (28)	11 (11)$^{\#}$	9 (9)$^{\#}$	16.22	0.000

[Groups A, B and C: normal saline, ephedrine and phenylephrine, respectively. Level of significance: Compared with Gr. A, $^{\#}P$ <0.05]

Table 4 — BIS values ($\bar{x} \pm s$)

Gr.	T0	T1	T2	T3	T4	T5
A	94.2±6.5	41.4±4.6*	48.5±6.1*	45.3±5.8*	45.7±5.7*	46.2±6.4*
B	94.6±6.3	45.9±5.1*$^{\#}$	60.4±6.5*$^{\#}$	58.5±12.8*$^{\#}$	59.4±12.5*$^{\#}$	56.5±12.9*$^{\#}$
C	94.3±6.7	42.2±4.3*	47.3±6.4*	46.2±6.6*	45.8±5.9*	45.3±5.2*

[Groups A, B and C: normal saline, ephedrine and phenylephrine, respectively. Level of significance: Compared with T0, *P <0.05; compared with Gr. A, $^{\#}P$ <0.05]

Table 5 — BIS recovery and anesthesia recovery times ($\bar{x} \pm s$)

Index	Groups (n=100)			F value	P value
	A	B	C		
BIS recovery to 65	7.4±0.8	6.9±0.7$^{\#}$	7.6±0.9	8.51	0.129
BIS recovery to 75	8.8±1.0	7.5±0.9$^{\#}$	9.0±1.0	7.34	0.142
BIS recovery to 85	13.5±1.2	13.1±1.1	13.9±1.2	2.68	0.787
BIS recovery to 95	15.5±1.3	15.8±1.2	15.3±1.3	3.74	0.751
Respiratory recovery	11.6±1.0	10.5±0.9	11.9±1.3	5.48	0.263
Consciousness recovery	14.5±1.2	14.1±1.4	14.7±1.3	2.83	0.772
Extubation time	16.5±1.5	16.2±1.8	16.8±1.6	1.56	0.845

[Groups A, B and C: normal saline, ephedrine and phenylephrine, respectively. Level of significance: Compared with Gr. A, $^{\#}P$ <0.05]

Discussion

Hypotension is a common complication during surgical anesthesia. Persistent hypotension during elective major abdominal surgery is reported to be a significant risk factor for postoperative complications which may result in prolonged hospitalization and impact patient outcomes[5]. Sakata *et al*.[6] found that continuous perioperative hypotension was an important risk factor for postoperative cardiovascular and cerebrovascular accidents. Therefore, actively seeking preventive measures that can reduce intraoperative hypotension and stabilize hemodynamic parameters are of great importance to the prognosis of patients undergoing lower abdominal surgery.

Ephedrine and phenylephrine are commonly used as pressors during surgery[7]. Ephedrine can directly or indirectly act on α, β adrenergic receptors, and increase blood pressure, cardiac output and stroke volume, with significant pressor effects, which can last the entire observation period. However, it can also increase peripheral vascular resistance and accelerate heart rate while increasing blood pressure[8,9]. Phenylephrine acts only on α-adrenergic receptors, which can raise blood pressure and increase peripheral vascular resistance through agonizing effects on α-receptors, and at the same time reflexively cause a decrease in heart rate and reduce cardiac output[10,11]. This study compared the changes in hemodynamic parameters of patients after pre-injection of the two drugs, and found that both ephedrine and phenylephrine could significantly increase blood pressure (SBP, DBP, MAP) during surgery, and that ephedrine had a larger increase range, longer action time, and increased CO, but also with the increase of HR, while phenylephrine increased blood pressure accompanied by a decrease in HR, the rise of SVR, but the impact of both on HR did not exceed the normal range.

Effective control of postoperative adverse reactions is of great significance to the postoperative recovery of patients, which can help them pass the recovery period smoothly, reduce complications, and benefit the recovery[12]. To clarify whether the pre-injection of pressors can produce adverse reactions while increasing the perioperative blood pressure of patients, this study compared the adverse reactions that may occur after surgery in the three groups of patients. It was found that the incidence of hypotension in the group without pre-injection of pressors was significantly higher than that in the two groups with pre-injection of pressors. Although pre-injection of ephedrine may cause postoperative tachycardia, pre-injection of phenylephrine may cause adverse reactions such as bradycardia, but the differences were not statistically significant. Taken together, pre-injection of pressors can significantly reduce postoperative adverse reactions.

BIS is an index reflecting the functional status of cerebral cortex, which can effectively monitor the depth of anesthesia and the state of consciousness of patients during general anesthesia[13]. It is indicated by 0-100 points, of which 40-65 is anesthesia state and BIS of >65 indicate shallow anesthesia[14]. In this study, all patients in the three groups were in the range of normal anesthesia at T1-T5, in which the BIS value of the ephedrine pre-injection group was significantly increased, which may be related to the increase of CO caused by ephedrine. Xia *et al*.[15] also found that BIS increased with the rise of cardiac output after intravenous administration of ephedrine. In view of this situation, the depth of anesthesia can be appropriately deepened while raising blood pressure during surgery.

To further explore the safety and reliability of the pre-injection of pressors, the recovery time of BIS value and resuscitation time of three groups were compared. It was found that after the target-controlled infusion was stopped in each group, the time of BIS value recovery to 65-75 was significantly shorter in the ephedrine pre-injection group than that in the non-injection group. There were no significant differences in the recovery of BIS value to 85, 95 and the time of recovery of breath, mind and extubation, but there was no significant difference between the two groups. Hence, pre-injection of pressors before anesthesia did not exert adverse effects on postoperative resuscitation.

Conclusion

Results of the above study indicate that pre-injection of ephedrine and phenylephrine during anesthesia increases blood pressure and thereby reduces the incidence rate of adverse reactions, without compromising patients' self-awareness and respiratory recovery. It has clearly demonstrated that appropriate pre-injection of pressors can effectively prevent and control perioperative hypotension, which is conducive to postoperative safety of patients and thus of reference value for clinical use.

Conflict of interest

Authors declare no competing interests.

References

1 Ma RX, Qiao RQ, Xu MY, Li RF & Hu YC, Application of Controlled Hypotension During Surgery for Spinal Metastasis. *Technol Cancer Res Treat*, 21 (2022) 15330338221105718.

2 Chen W, Huang H, Yang C, Hu X, Bao F & Jiang H, Preoperative Low-dose and High-dose Pregabalin and Cardiovascular Response to Endotracheal Intubation: A Prospective, Randomized, Single-blind, Controlled Study in China. *Clin Ther*, 41 (2019) 68.

3 Elagamy AE, Kamaly AM, Shahin MI & Saleh M, Norepinephrine versus ephedrine for hypotension prophylaxis during cesarean section under spinal anesthesia. *Ain-Shams J Anesthesiol*, 13 (2021) 1. https://doi.org/10.1186/s42077-020-00124-4.

4 Yancey R, Anesthetic Management of the Hypertensive Patient: Part I, *Anesth Prog*, 65 (2018) 131.

5 Tassoudis V, Vretzakis G, Petsiti A, Stamatiou G, Bouzia K, Melekos M & Tzovaras G, Impact of intraoperative hypotension on hospital stay in major abdominal surgery. *J Anesth*, 25 (2011) 492. doi: 10.1007/s00540-011-1152-1.

6 Sakata K, Yoshimura N, Tanabe K, Kito K, Nagase K & Iida H, Prediction of hypotension during spinal anesthesia for elective cesarean section by altered heart rate variability induced by postural change. *Int J Obstet Anesth*, 29 (2017) 34.

7 Pournajafian A, Rokhtabnak F, Ghodrati M, Kholdebarin A, Hassani A & Dayani A, Comparison of the effect of phenylephrine and ephedrine on the neonate in treatment of hypotension due to spinal anesthesia in pregnant women candidate for cesarean section. *Iran J Obstet Gynecol Infert,* 23 (2020) 7.

8 Quan AT & Li F, Hyperinflation of Vasopressors (Vasopressin, Norepinephrine, Ephedrine, etc), *J Pharm Pract*, 31 (2018) 399.

9 Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, Bertran S, Leone M, Pastene, Piriou V & Molliex S, Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*, 318 (2017) 1346.

10 Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G & Wunsch H, Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA*, 317 (2017) 1433.

11 Eikelis N, Marques FZ, Hering D, Marusic P, Head GA, Walton AS, Lambert EA, Esler MD, Sari CI, Schlaich MP & Lambert GW, A polymorphism in the noradrenaline transporter gene is associated with increased blood pressure in patients with resistant hypertension, *J Hypertens*, 36 (2018) 1571.

12 Jiang Q, Zhang R & Liu T, Effect of nalbuphine on patient controlled intravenous analgesia after radical resection of colon cancer. *Oncol Lett*, 19 (2020) 2533.

13 Sun J, Liu Z, Rolls ET, Chen Q, Yao Y, Yang W, Wei D, Zhang Q, Zhang J, Feng J & Qiu J, Verbal creativity correlates with the temporal variability of brain networks during the resting state. *Cereb Cortex*, 29 (2019) 1047.

14 Dong L, Chen L, Shi T, Wei M, Zhang HZ, Li YP, She L & Yan ZC, Combined monitoring of intracranial pressure and bispectral index in patients with severe craniocerebral trauma post-operatively. *Clin Neurol Neurosurg*, 148 (2016) 42.

15 Xia J, Sun Y, Yuan J, Lu X, Peng Z & Yin N, Hemodynamic effects of ephedrine and phenylephrine bolus injection in patients in the prone position under general anesthesia for lumbar spinal surgery. *Exp Ther Med*, 12 (2016) 1141.