Endokrynologia Polska
DOI: 10.5603/EP.a2021.0004
Volume/Tom 72; Number/Numer 2/2021
ISSN 0423–104X, e-ISSN 2299–8306

An assessment of the effectiveness of regional analgesia after VATS measured by an objective method for assessing testosterone, cortisol, α-amylase, sIgA, and β-endorphin levels — a randomised controlled trial

Szymon Bialka[1], Magdalena Sliwczynska[1], Aleksandra Marciniak[1], Damian Czyzewski[2], Hanna Misiolek[1]

[1]*Department of Anaesthesiology, Intensive Care, and Emergency Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland*
[2]*Chair and Department of Thoracic Surgery, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Zabrze, Poland*

Abstract

Introduction: Thoracic surgeries are associated with intense postoperative pain. General opioid analgesia is still the main anaesthetic method. Due to the large number of opioid-induced side effects, alternative methods of pain relief are sought. One of them is the use of balanced analgesia, which consists of regional analgesia, non-opioid painkillers, and small doses of opioids.

Material and methods: The objective of this study was to assess the effectiveness of preoperative thoracic paravertebral block (ThPVB) in the treatment of postoperative pain after video-assisted thoracic surgery (VATS) by measuring hormone levels in blood serum or saliva. It was a randomised, open-label study conducted in a single university hospital setting between May 2018 and September 2019. In total, 119 patients were scheduled for elective video-assisted thoracic surgery. Performed interventions included: preoperative thoracic paravertebral block with 0.5% bupivacaine, followed by postoperative oxycodone combined with nonopioid analgesics. Follow-up period comprised first 24 hours and one, two, and six months after surgery. Main outcomes were measured by pain intensity assessed using the Numerical Rating Scale (NRS) and the levels of the following hormones: testosterone, cortisol, α-amylase activity, sIgA, and β-endorphin.

Results: A total of 119 patients were randomised into two groups and, of these, 49 were subsequently excluded from the analysis. The final analysis included 37 patients from the study group and 33 from the control group. There were no statistically significant differences in the analysed parameters the relative change T1–T0. There was a tendency towards statistical significance in the relative change T2–T0 in testosterone levels. At rest, no statistically significant differences were found between groups and time in the percentage of patients with NRS ≥ 1. During cough, the percentage of patients with NRS ≥ 1 was higher at T1 and T2 time points in the ThPVB group. Of the factors considered, only α-amylase levels statistically significantly increased the chance for higher NRS score after a month [OR = 1.013; 95% PU: 1.001–1.025; $p < 0.01$].

Conclusions: ThPVB is effective and safe for patients undergoing VATS. It can be an effective alternative for general anaesthesia using high doses of opioids. **(Endokrynol Pol 2021; 72 (2): 133–142)**

Key words: *NRS; video-assisted thoracic surgery; acute pain; regional anaesthesia; testosterone; cortisol; α-amylase; sIgA; β-endorphin*

Introduction

Thoracic surgeries are usually associated with intense postoperative pain. Intraoperative tissue damage occurs mainly in the periosteum and pleura, which are very richly innervated with rami from the intercostal nerves, diaphragmatic nerve, and sympathetic trunk [1].

If not treated properly, postoperative pain may cause many complications. Sympathetic and neuroendocrine activation occurs. It has a deep negative influence on cardiovascular and respiratory systems. Neuroplastic changes in the central nervous system may cause chronic postoperative hyperalgesia [2]. Thoracic procedures are among those that frequently cause chronic pain syndromes. Persistent acute postoperative pain [3] not treated properly is the main risk factor. Adequate analgesia is a very important part of the therapeutic process and has significant influence on its outcome.

Video-assisted thoracoscopic surgery (VATS) is among the most common thoracic surgical procedures. VATS can be diagnostic or therapeutic. It is less invasive than classic thoracotomy and is associated with fewer complications [4] and lower-grade postoperative pain. Nevertheless, adequate analgesia may sometimes be challenging. Lately, oxycodone is one of the most frequently used opiates. It is pure agonist of MOR, DOR, and KOR opiate receptors. It has a very strong therapeutic effect and is safe (especially administered in patient-controlled analgesia — PCA method). In most of the cases, it is advisable to combine regional anaes-

Szymon Bialka MD, PhD, Department of Anaesthesiology, Intensive Care, and Emergency Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, 41–800 Zabrze, Poland, tel: (+48) 323 704 593; e-mail: szymon.bialka@gmail.com

thesia (RA) techniques with opiates and nonsteroidal anti-inflammatory drugs (NSAIDs). Thoracic paravertebral block (TPVB) is one of the most popular and well described RA techniques. Thoracic paravertebral block requires administration of a local anaesthetic solution into the paravertebral space on the thoracic level. It is possible to anaesthetise the roots and rami of spinal nerves, pre- and postganglionic fibres, sympathetic nervous system, and proximal intercostal nerves. The block is unilateral — sensory, motor, and sympathetic. Effective TPVB with intravenous (*i.v.*) opiates and/or NSAIDs is state-of-the-art multimodal analgesia [5, 6], which minimises perioperative stress level in the patient.

It is possible to measure stress reaction, and therefore the quality of perioperative analgesia. One of the methods is to assess plasma and saliva levels of various endogenous substances that can be used as a measure of endogenous adrenergic activity. These include β-endorphin, secretory immunoglobulin A (SIgA), cortisol, testosterone, salivary α-amylase, and many more. Beta-endorphins are produced in the anterior pituitary gland. The substrate is proopiomelanocortin. Proopiomelanocortin is synthesised in response to corticoliberin, which is released from the hypothalamus as a reaction to stress or pain [7]. Beta-endorphins have an analgesic effect by binding to opioid receptors, mostly the mu-opioid receptors (MORs). This inhibits the release of tachykinins, mainly the P substance, and therefore blocks the conduction of pain stimuli. In the central nervous system, binding of β-endorphins to MORs causes release of gamma-aminobutyric acid (GABA), which is a well-known inhibitory neurotransmitter [8]. Secretory immunoglobulin A (SIgA) is an antibody that can be found on the surface of mucous and serous membranes. Because its levels drop during stress, it can be used to assess the body's response to pain [9]. Cortisol is a natural steroid hormone, often referred to as the stress hormone. It is the final product of stimulation of the hypothalamic–pituitary–adrenal axis (the HPA axis). The stimulation occurs in response to stress. Cortisol has many effects on metabolism [10]. The next substance is salivary α-amylase. It is an enzyme produced by salivary gland cells, and its levels are well correlated with the activity of the sympathetic nervous system — they increase as a part of stress response. Studies have shown that it is a reliable marker of the sympathetic nervous system response to stress stimuli [10]. Testosterone is the primary male steroid sex hormone belonging to the androgen hormone group. Endorphins secreted during pain or stress reduce testosterone levels by inhibiting the synthesis of gonadotropic hormone (GnRH), as well as by inhibiting the production of testosterone by Leydig interstitial cells in the testes [11]. Therefore, testosterone plasma levels are lower during stress and pain, chronic in particular [12].

The primary endpoint was evaluation measuring plasma or saliva levels of described hormones as well as measuring pain on the NRS scale in the perioperative period depending on the analgesia used after VATS.

Material and methods

This randomised, observational study was conducted in the Medical University of Silesia, Poland. With the approval of the Institutional Review Board (No. KNW/0022/KB1/138/I/17/18 of 13.03.2018) and after obtaining written informed consents, we enrolled 119 patients scheduled for elective VATS between May 2018 and September 2019. The study was registered on ClinicalTrials.gov under No. NCT04414488. All patients were aged between 18 and 75 years, had a body mass index between 19–30 kg/m^2, and had American Society of Anesthesiology (ASA) physical status between I and III. Lack of consent, significant coagulopathy, contraindication to ThPVB or drugs used in the protocol, history of chronic pain, chest wall neoplastic invasion, previous thoracic spine surgery, mental state preventing effective use of PCA device, and renal failure (GFR < 60 mL/min/1.73 m^2) were exclusion criteria.

Protocol

Patients were randomly assigned to one of two groups receiving different postoperative analgesic regimens:

— patient-controlled analgesia with oxycodone (control group);
— thoracic paravertebral block plus patient-controlled analgesia with oxycodone (ThPVB group).

Randomisation without stratification was based on computer-generated codes, which were kept in sequentially numbered opaque envelopes.

All patients were premedicated with oral midazolam at an adequate dose.

Fentanyl (FENTANYL WZF, Polfa Warszawa S.A., Poland) was used for surgical analgesia in both groups. Fentanyl at 1.5 μgkg^{-1}, followed by fractional doses of 1 to 3 μgkg^{-1} if heart rate (HR) or mean blood pressure rose more than 20% above the base-line value obtained just before surgery onset, was used for induction of anaesthesia.

In the ThPVB group, a single-shot ThPVB was performed at the Th3 to Th4 level, approximately 2.5 to 3 cm lateral to the tip of the spinous process before the induction of general anaesthesia. A pre-block ultrasound examination was performed to assess the depth of the transverse process and the pleura. An insulated 10-cm-long needle was used, and this was connected to a peripheral nerve stimulator with an initial set current of 2.5 mA. The current was gradually reduced as the needle was inserted until the appearance of visible intercostal muscle activity with a current of 0.3 to 0.5mA (paravertebral space identification). Plain bupivacaine (0.3 mL kg^{-1}) was then injected after a negative aspiration test for air or blood. The efficacy of the blockade to cold was checked after 20 min with a plastic ampoule of saline stored in the freezer. Testing was symmetrical on both sides of the thorax. A difference in the sensation to cold between the blocked and unblocked sides was checked to confirm an effective block.

General anaesthesia was induced in both groups with midazolam 0.1 mgkg^{-1}, propofol 2 mgkg^{-1}, and cisatracurium 0.15 mgkg^{-1}. Patients were intubated using a left-sided double lumen tube of an adequate size. Patients were then arranged in a lateral position. Anaesthesia was maintained with one minimal alveolar concentration (MAC1) sevoflurane. Patients awoke from anaesthesia in the post-anaesthesia care unit (PACU), where extubation was performed by an anaesthetist after administration of incremental doses of atropine and neostigmine, as required.

The postoperative pain management regimen was identical in both groups. Patients complaining of postoperative pain were given *i.v.* oxycodone by an anaesthetist before commencing the patient-controlled analgesia (PCA). This dose was titrated to achieve adequate analgesia or until side effects occurred. Each patient then commenced PCA. The PCA solution was oxycodone (1 mgmL^{-1}) and the PCA was programmed to allow a self-administered bolus dose of 1 mg oxycodone with a lockout time of 5 min. During the night, the basal rate oxycodone was 2–4 mg per hour. Additionally, patients were given 1 g intravenous paracetamol every 6 hours and 100 mg of intravenous ketoprofen every 12 hours, if needed.

Measurements

Demographic parameters such as age, sex, height, weight, BMI, as well as heart rate and blood pressure were recorded before surgery. After qualification for the study, blood and saliva samples were taken from each patient to determine the level of hormones: testosterone, cortisol, a-amylase activity, sIgA, and b-endorphin (T0). During anaesthesia, all patients were monitored: electrocardiography (3-lead), heart rate (HR; 1/bpm), non-invasive blood pressure (NIBP; mm Hg), end-expiratory carbon dioxide (EtCO2: mmHg) and sevoflurane (EtSev), and arterial blood saturation measured by pulse oximetry.

In the immediate postoperative period and the first 24 hours after surgery, the following data were recorded: heart rate (HR; 1/bpm) and arterial blood saturation measured by continuous pulse oximetry. Non-invasive blood pressure measurements and NRS pain levels were recorded every 6 hours. Six hours (T1) and 24 hours (T2) after surgery, each patient had their blood and saliva re-tested for hormone levels. Additionally, one, three, and six months after surgery, a telephone follow-up was performed and pain levels were determined on the NRS scale.

Obtaining material for biochemical assays

Saliva was collected from participants in order to perform laboratory tests, using a special disposable Salivette tube (Sarstedt AG & Co., Germany). Saliva was collected by placing a sterile tampon under the tongue or chewing it for 30–45 seconds. The soaked saliva pad was then placed in a suspended insert with a perforated bottom. The insert with the tampon was placed in a centrifuge tube and closed with a stopper. Next, the tube was centrifuged (1000 × g for 10 min) to obtain a ready-to-test saliva supernatant. Approximately 0.7 mL of the supernatant from every sample collected was used for further testing. Samples were frozen after centrifugation at –85°C until performing laboratory tests.

At the same time, blood was collected for laboratory tests from the ulnar vein. Blood for testing was collected using disposable equipment in a volume of 5 mL into a tube containing EDTA and aprotinin. Next, the tube was centrifuged (1000 × g for 5 min). After centrifugation and separation of morphotic elements, the obtained plasma was divided into two tubes and frozen at –85°C until laboratory tests were performed.

Biochemical analysis

Determination of alpha-amylase activity

Alpha-amylase activity assay was performed by a static method with an AMYLAZA kit (Aqua-Med Łodz, Poland). The samples were diluted 100 times using 0.9% chloride solution. This method uses 2-chloro-4-nitrofenylo-maltotrioside as a substrate. The reaction was performed in pH 6.0 MES buffer at 37°C, yielding a coloured reaction product. The product was then analysed via spectrophotometry at 405 nm. Results are expressed in salivary a-amylase activity units (U/mL). Measurement imprecision of the method was 4.1%.

Determination of cortisol and testosterone levels

Commercial ELISA (Diapra, Italy) was used to determine the levels of cortisol and testosterone. The analytical procedure was in accordance with the manufacturer's instructions provided in the technical manuals supplied with the kits. Absorbance readings were taken using a μQuant reader (Biotek, USA), while results were processed using KCJunior (Biotek, USA). The sensitivity of the method was 0.12 ng/mL for cortisol and 3.28 pg/mL for testosterone. The method's imprecision was 6.2% and 7.9%, respectively.

Determination of sIgA concentration

Commercial ELISA kits (Immunodiagnostic AG, Germany) were used to determine the levels of sIgA. The analytical procedure was in accordance with the manufacturer's instructions provided in the technical manuals supplied with the kits. Absorbance readings were taken using a μQuant reader (Biotek, USA), while results were processed using KCJunior (Biotek, USA).

Determination of β-endorphin levels

Determination of b-endorphin levels was preceded by extraction on C18 Sep-Pak columns containing 50 mg C18, using trifluoroacetic acid (TFA) and elution buffer (i.e. 60% acetonitrile, 1% TFA, and 39% distilled water). The extracts obtained were lyophilised. To determine the levels of b-endorphins in the tested samples, lyophilisates were dissolved in an appropriate amount of buffer, and then commercial ELISA tests from Elabscience (USA) were used. The analytical procedure was in accordance with the manufacturer's instructions provided in the technical manuals supplied with the kits. Absorbance readings were taken using a μQuant reader (Biotek, USA), while results were processed using KCJunior (Biotek, USA).

Statistical analysis

Data on interval scale with a normal distribution were presented as mean ± standard deviation (SD), while data with a distribution deviating from the normal distribution were presented as the median and lower and upper quartiles. The normality of the distribution was assessed with the Shapiro-Wilk test and the quantile plot. Qualitative data are presented as numbers and percentages. In order to compare the variables on the nominal and ordinal scales, the χ^2 test was used. Comparison of two independent groups was carried out using Student's t-test for data with a distribution similar to normal or the U Mann-Whitney test in other cases. Data on the NRS scale were compared using the χ^2 test and the McNemara test (change in observation between T2 and T1 time). In the case of data analysis on a point scale, the Wilcoxon pairwise test was used. Time analysis of biochemical parameters was performed using mixed model analysis with contrast analysis with Benjamini-Hochberg correction for multiple comparisons. In the case of data deviating from the normal distribution, rank analysis of mixed models was used. Factors influencing the values of the NRS scale ≥ 1 were determined on the basis of univariate and multivariate logistic regression. The parameters were considered statistically significant when $p < 0.05$. The calculations were made using the following programmes: Statistica 13.0 (TIBCO Inc., Palo Alto, CA, U.S.) PL version, Excel of the MS Office suite, and the R (CRAN) environment.

Results

During the study period, 119 patients underwent VATS and were screened for this study. In total, 110 patients met the inclusion and exclusion criteria and were randomly assigned to the two study groups, with 55 patients in each group. Overall, 25 patients were excluded after randomisation: 13 patients from the ThPVB group (seven had conversion to thoracotomy; six had ineffective ThPVB) and 12 patients

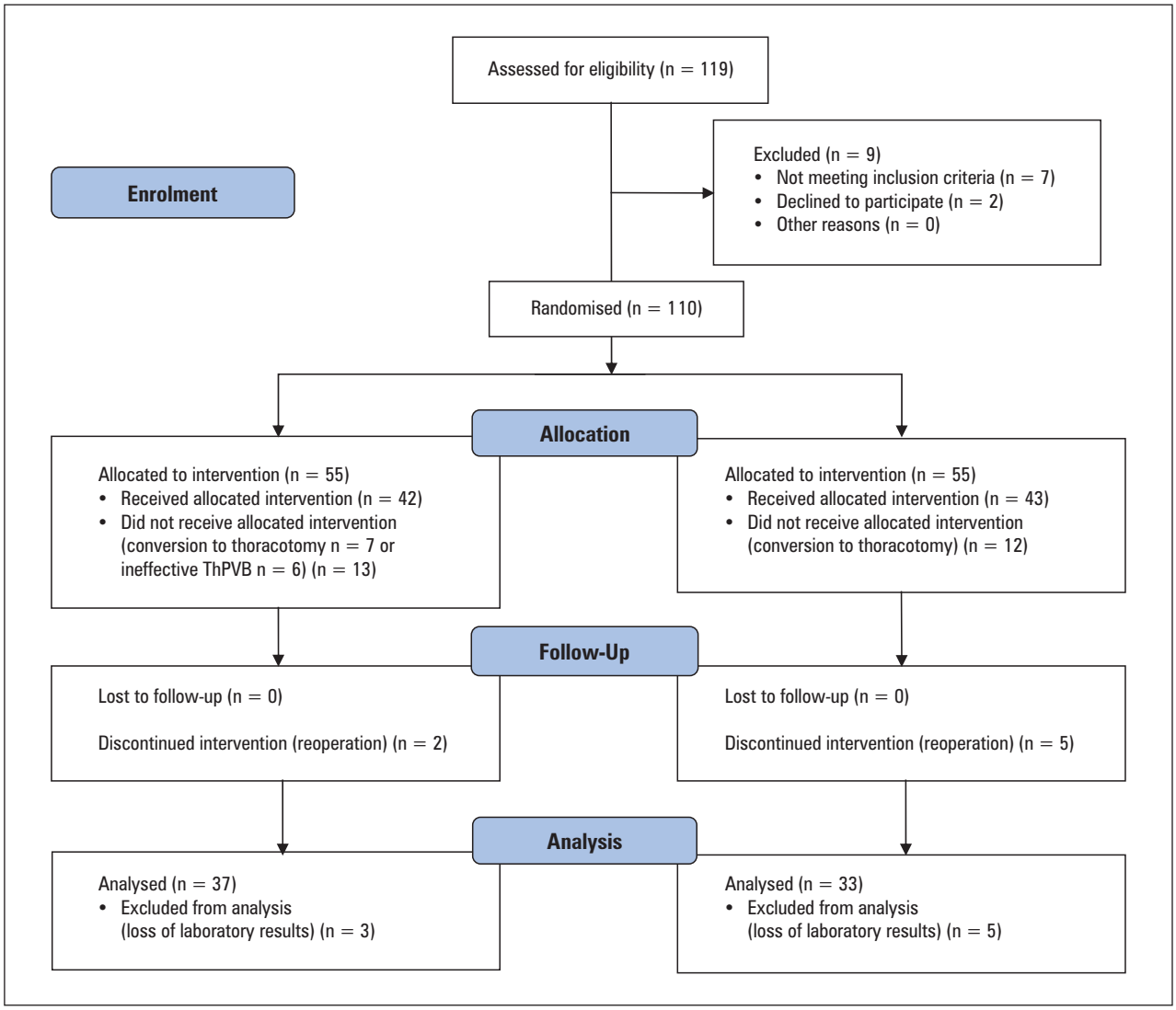

Figure 1. *Consort flow diagram*

from the control group (conversion to thoracotomy) (Fig. 1). Finally, 70 patients (33 men and 37 women) aged 62 ± 14 years and with a BMI of 27.4 ± 4.5 kg/m^2 completed the study. There were no significant differences between groups in gender, age, height, BMI, or ASA physical status. Moreover, no differences were found for surgery time and the operated site. Only lobectomy was statistically more frequent in the ThPVB group. The demographics and main clinical findings are presented in Table 1.

There were no statistically significant differences in the parameters analysed in the relative change T1–T0 (Tab. 2). There was a tendency towards statistical significance in the relative change T2–T0 in testosterone levels, with higher values observed in the ThPVB group (Tab. 3).

At rest, no statistically significant differences were found between the groups and time points in the percentage of patients with NRS ≥ 1 point. During cough, the percentage of patients with NRS ≥ 1 was higher at T1 and T2 in the ThPVB group. Simultaneously, a statistically significant reduction in the percentage of these patients over time was also observed in the ThPVB group. There were no significant differences in NRS scores during cough between the groups and, similarly, a significant reduction in NRS at T2 was observed in the ThPVB group. No significant differences were found between the groups in the percentage of people with NRS ≥ 1 during a follow-up after one, two, and six months (Tab. 4).

The analysis of β-endorphin, cortisol, sIgA, and α-amylase levels showed a statistically significant effect of time rather than the group on the levels of measured hormones. At the T2 time point, statistically significantly higher cortisol levels were found in the ThPVB group. A summary of descriptive statistics and ANOVA analysis, as well as the levels of measured hormones, are presented in Table 5 and 6.

Table 1. *Patient demographic characteristics*

Variables	ThPVB group (n = 37) (52.9%)	Control group (n = 33) (47.1%)	p
Female/Male N (%)	21/16 (56.8/43.2)	16/17 (48.5/51.5)	0.49
Lobectomy N (%)	25 (67.6)	12 (36.45)	< 0.05
Wedge resection N (%)	8 (21.6)	9 (27.3)	
Other N (%)	4 (10.8)	12 (36.45)	
Operated side R/L N (%)	18/19 (48.6/51.4)	23/10 (69.7/30.3)	0.07
Surgery time [min]	115.0 ± 45.8	103.6 ± 58.0	0.36
Age [yrs]	64 ± 11	61 ± 17	0.48
Weight [kg]	75.2 ± 12.0	79.3 ± 15.8	0.23
BMI [kg/m^2]	27.1 ± 4.3	28.0 ± 5.0	0.44
Height [m]	1.63±0.07	1.65±0.08	0.13
ASA class [I/II/III] (N)	2/22/13	2/19/12	0.49

Data are n, mean ± SD or %. ASA — American Society of Anaesthesiologists; L — left; R — right

Table 2. *Comparison of relative changes in the analysed parameters between T1 and T0 in both groups*

Variables	Δ relative (%) T_1–T_0		p
	ThPVB group	Control group	
β-endorphin	131.7 ± 103.1	104.6 ± 88.34	0.24
Cortisol	63.5 (–18.6–145.9)	12.7 (–17.6–151.5)	0.79
Testosterone	44.8 (12.6–147.3)	19.2 (3.2–64.8)	0.20
sIgA	–6.1 (–16.3–16.9)	9.5 (–16.6–39.3)	0.38
α-amylase	29.5 (20.3–51.9)	37.2 (26.6–63.3)	0.29
SBP	–13.9 (–22.4– –7.1)	–10.0 (–19.6– –4.0)	0.37
DBP	–12.6 (–20.0–3.3)	–12.5 (–22.1– –1.3)	0.80
MBP	–12.8 (–20.4– –3.1)	–12.5 (–19.2– –4.0)	0.98
HR	3.8 (–8.7–14.3)	0 (–6.2–4.8)	0.23

Data are Δ relative (%) T1–T0. sIgA — secretory immunoglobulin A; SBP — systolic blood pressure; DBP — diastolic blood pressure; MBP — mean blood pressure; HR — heart rate

Table 3. *Comparison of relative changes in analysed parameters between T2 and T0 in both groups*

Variables	Δ relative (%) T_1–T_0		p
	ThPVB group	Control group	
β-endorphin	198.3 ± 112.8	199.6 ± 124.5	0.96
Cortisol	35.3 (–22.7–107.6)	23.6 (–30.8–62.8)	0.11
Testosterone	30.60 (0.90–96.71)	5.82 (–6.42–30.34)	0.06
sIgA	14.53 (2.97–26.98)	12.66 (4.47–41.56)	0.32
α-amylase	26.58 (14.12–53.81)	45.09 (11.70–88.04)	0.26
SBP	–13.2 (–18.6– –4.6)	–11.7 (–22.6– –2.0)	0.91
DBP	–13.3 (–22.1–0)	–12.5 (–18.9– –7.5)	0.75
MBP	–11.2 (–22.1– –6.0)	–12.7 (–17.3– –2.4)	0.98
HR	–1.4 (–8.9–13.0)	4.2 (–5.6–8.6)	0.57

Data are Δ relative (%) T2–T0; sIgA — secretory immunoglobulin A; SBP — systolic blood pressure; DBP — diastolic blood pressure; MBP — mean blood pressure; HR — heart rate

Table 4. *Comparison of NRS scores between the groups*

NRS ≥ 1	ThPVB n = 37 (52.9%)	Control n = 33 (47.1%)	p
At rest			
T0 [N (%)]	0	0	–
T1 [N (%)]	19 (51.3)	15 (45.4)	0.62
T2 [N (%)]	14 (37.8)	8 (24.2)	0.22
p*	0.57	0.07	
During cough			
T0 [N (%)]	0	0	–
T1 [N (%)]	34 (91.9)	21 (63.6)	< 0.01
T2 [N (%)]	28 (75.7)	17 (51.5)	< 0.05
p*	< 0.001	0.44	
T1 [point]	3 (2–5)	1 (1–3)	0.10
T2 [point]	2 (0–5)	1 (0–3)	0.26
p#	< 0.01	0.10	
NRS ≥ 1			
1 month	23 (62.2)	23 (69.7)	0.51
2 months	8 (21.6)	7 (21.2)	0.97
6 months	5 (13.5)	5 (15.2)	1.00

p* — McNemar; p# — Wilcoxon signed-rank test

Table 5. *Descriptive statistics in the study groups in time for the levels of β-endorphin, cortisol, testosterone, sIgA, and α-amylases*

Group	Time	N	Mean	SD	Min	Max	Q_1	Me	Q_3
β-endorphin [pg/mL]									
ThPVB	T0	37	5.30	1.81	2.33	10.23	4.14	4.73	6.21
	T1	37	11.63	5.22	4.39	23.45	7.29	10.99	15.83
	T2	37	14.39	4.11	2.25	21.23	12.36	15.43	17.62
Control	T0	33	5.25	1.96	2.29	11.23	4.01	4.87	6.45
	T1	33	10.33	5.00	2.18	22.18	6.47	10.18	11.40
	T2	33	14.41	4.48	3.89	21.36	11.11	14.35	18.19
Cortisol [ng/mL]									
ThPVB	T0	37	12.22	3.86	7.06	21.90	9.20	11.20	13.76
	T1	37	19.54	8.69	7.34	35.80	10.50	21.30	27.40
	T2	37	16.76	7.19	7.33	34.10	9.89	16.70	20.10
Control	T0	33	12.08	3.16	6.21	17.89	9.59	11.74	14.25
	T1	33	18.86	9.75	7.29	38.10	10.30	14.55	27.60
	T2	33	13.47	5.75	7.34	30.10	8.87	11.22	17.80
Testosterone [pg/mL]									
ThPVB	T0	37	64.54	45.29	10.13	189.30	25.24	48.93	94.53
	T1	37	94.67	49.12	31.28	223.46	59.72	73.48	125.10
	T2	37	84.83	46.16	27.81	233.12	50.12	71.23	118.20

→

Table 5. *Descriptive statistics in the study groups in time for the levels of β-endorphin, cortisol, testosterone, sIgA, and α-amylases*

Group	Time	N	Mean	SD	Min	Max	Q_1	Me	Q_3
	T0	33	76.31	51.02	10.15	195.20	43.81	54.21	100.34
Control	T1	33	103.26	57.72	21.50	231.36	49.86	97.60	153.20
	T2	33	86.43	46.41	27.64	183.20	44.36	69.81	122.13
sIgA [ug/mL]									
	T0	37	112.94	13.06	75.56	130.22	102.54	115.98	123.07
ThPVB	T1	37	115.56	21.37	88.41	206.81	100.56	112.35	120.18
	T2	37	131.41	15.78	71.34	174.38	125.43	130.02	136.71
	T0	33	111.77	15.29	69.88	133.47	103.61	110.91	125.61
Control	T1	33	120.79	26.46	76.59	177.56	100.22	118.93	132.74
	T2	33	138.48	19.83	110.75	189.71	128.56	131.25	144.32
α-amylases [U/mL]									
	T0	37	91.10	28.13	6.59	126.70	76.18	99.89	108.45
ThPVB	T1	37	126.53	51.71	11.38	267.82	100.04	135.05	141.69
	T2	37	122.04	39.39	10.92	200.13	99.83	122.84	145.38
	T0	33	91.09	26.89	9.20	135.13	76.54	97.21	105.34
Control	T1	33	132.60	46.69	14.56	224.79	113.26	134.51	155.72
	T2	33	134.24	47.22	17.63	215.10	105.68	133.28	166.25

Data are: mean ± SD, n; Min — minimum; Q_1 — lower quartile; Me — median; Q_3 — upper quartile; Max — maximum

Table 6. *ANOVA analysis results with contrast analysis for β-endorphin, cortisol, testosterone, sIgA, and α-amylase levels*

Anova	p	Time	p_{Group}	Group	P_{Time}		$T_{0–1}$	$T_{0–2}$	$T_{1–2}$
β-endorphin [pg/mL]									
Group	0.46	T0	0.79	ThPVB	< 0.001	ThPVB	< 0.001	< 0.001	< 0.01
Time	< 0.001	T1	0.23	Control	< 0.001	Control	< 0.001	< 0.001	< 0.001
Interaction	0.39	T2	0.98						
Cortisol [ng/mL]									
Group	0.22	T0	0.98	ThPVB	< 0.001	ThPVB	< 0.001	< 0.01	< 0.01
Time	< 0.001	T1	0.61	Control	< 0.01	Control	< 0.01	0.46	< 0.001
Interaction	0.21	T2	< 0.05						
Testosterone [pg/mL]									
Group	0.60	T0	0.29	ThPVB	< 0.001	ThPVB	< 0.001	< 0.001	< 0.01
Time	< 0.001	T1	080	Control	< 0.001	Control	< 0.001	< 0.05	< 0.001
Interaction	0.18	T2	0.89						
sIgA [ug/mL]									
Group	0.19	T0	0.98	ThPVB	< 0.001	ThPVB	0.95	< 0.001	< 0.001
Time	< 0.001	T1	0.17	Control	< 0.001	Control	0.20	< 0.001	< 0.001
Interaction	0.48	T2	0.28						
α-amylases [U/mL]									
Group	0.48	T0	0.99	ThPVB	< 0.001	ThPVB	< 0.001	< 0.001	0.49
Time	< 0.001	T1	0.61	Control	< 0.001	Control	< 0.001	< 0.001	0.79
Interaction	0.37	T2	0.24						

Of the considered factors such as test group, sex, type of surgery, operated side, use of rescue analgesia, BMI, NRS ≥ 1 (at rest and cough at T1), and levels of measured hormones (at T1), only alpha-amylase levels statistically significantly increased the chance for higher NRS score after a month (OR = 1.013; 95% PU: 1.001–1.025; $p < 0.01$).

Discussion

In our study, we measured plasma or saliva levels of specific substances produced during stress generated by a thoracic surgical procedure (VATS). We also measured perioperative pain levels with the numerical rating scale (NRS). Analgesia was obtained either with opiates alone or opiates plus regional anaesthesia (TPVB).

No statistically significant differences were found between groups and over time in the percentage of patients with NRS ≥ 1 during rest. During cough, the percentage of patients with NRS ≥ 1 was higher at T1 and T2 in the ThPVB group. Simultaneously, a statistically significant reduction in the percentage of these patients over time was also observed in the ThPVB group.

There were no significant differences between groups in terms of sex, age, height, BMI, or ASA physical status. Moreover, no differences were found for surgery time and operated site. The only difference was that lobectomy was statistically more frequent in the ThPVB group.

Many studies show that regional anaesthesia (ThPVB) has a positive effect during the perioperative period when compared with systemic opioids and NSAIDs. Terheggen et al. compared ThPVB with general anaesthesia (GE) for breast surgery. The results of this study demonstrated that thoracic PVB resulted in superior postoperative pain relief compared with GA when used for minor breast surgery [13]. Zhi et al. preformed a systematic review and a meta-analysis to check the effect of thoracic paravertebral block on thoracoscopic surgery. The authors concluded that thoracic paravertebral block contributes to pain control after thoracoscopic surgery, with reduced incidence of adverse effects like nausea and vomiting, atrial arrhythmias, drowsiness, hypotension, and pneumonia, compared to systemic analgesics [14–16].

Casati et al. compared ThPVB (continuous) with thoracic epidural for patients undergoing thoracotomy. They concluded that continuous thoracic paravertebral blockade is as effective as thoracic epidural in controlling postoperative pain and is associated with fewer haemodynamic side effects. Furthermore, ThPVB had a lower risk of failure [17].

Haager et al. compared regional anaesthesia (thoracic paravertebral block or thoracic epidural anaesthesia) with a systemic opioid administration (patient-controlled analgesia — PCA). The primary endpoint was the postoperative pain level measured with VAS at rest and during cough. The results showed that resting VAS values were similar for all groups, although they were higher but comparable during cough in patients with PCA, except for the period 8–16 hours after the procedure. Intraoperative sufentanil administration was significantly higher in patients with no regional anaesthesia performed. These results show that PCA for VATS-lobectomy could be an acceptable alternative for regional analgesia [18].

The results discussed above suggest that the efficacy of all compared techniques is similar in terms of postoperative analgesia. Nevertheless, regional anaesthesia allows the avoidance of some adverse effects that occur during systemic opioid administration.

In our study, we also assessed plasma or saliva levels of specific substances to measure stress reaction, and therefore the quality of perioperative analgesia. These were β-endorphin, secretory immunoglobulin A (SIgA), cortisol, testosterone, and salivary α-amylase. There were no statistically significant differences between the groups of patients, although there was a tendency towards statistical significance in the relative change (T2–T0) in testosterone levels, with higher values observed in the ThPVB group. The analysis of the levels of β-endorphin, cortisol, sIgA, and α-amylase showed statistically significant differences between time points but not between the groups. At T2, statistically significantly higher cortisol levels were found in the ThPVB group. Of the considered factors (such as: test group, sex, type of surgery, operated side, use of rescue analgesia, BMI, NRS ≥ 1 — at rest and during cough at T1) and hormone levels (at T1), only alpha-amylase levels statistically significantly predicted increased chance for higher NRS score a month after the surgery.

Miecznikowski et al. compared two effective therapeutic methods for patients with cervical spine dysfunction (CSD). Secretory immunoglobulin A (SIgA) was one of the analysed markers of pain and stress response. Results revealed a statistically significant influence of the type of therapy on sIgA levels. In both tested groups, the final levels of salivary sIgA were higher than the initial levels before the beginning of the treatment [19]. These results confirm the efficacy of used therapies. Zhi-Yang Chen et al. assessed plasma levels of endogenous opioid peptides (also β-endorphin) in a group of patients undergoing elective surgical procedures under intravenous general anaesthesia combined with an epidural blockade. Plasma levels of β-endorphin were significantly lower at all time points (20, 40, 60, and 80 minutes after surgery) when compared with the baseline values [20]. The results of this study confirm adequate level of the

used analgesic methods during the surgery. Shirasaki et al. attempted to evaluate the usefulness of a portable salivary alpha-amylase analyser. They tested patients with chronic low back or leg pain and pain-free patients undergoing elective surgery under general anaesthesia combined with epidural analgesia (control group). There was a statistically significant correlation between the VAS pain scale and salivary alpha-amylase levels. The authors suggested that this biomarker could be a useful indicator for the objective assessment of pain intensity [21]. Yardenia et al. compared three pain-management techniques in patients undergoing lower abdominal surgery. These techniques were: intermittent opiate regimen (IOR), patient-controlled analgesia (PCA), and patient-controlled epidural analgesia (PCEA). The authors measured cortisol and prolactin levels during the first 48 hours after the procedure. The results showed that patients in the PCEA group had reduced postoperative pain and therefore lower activation of the HPA axis. This study showed that cortisol levels are changed by postoperative pain [22]. Also, studies have shown that elevated plasma levels of cortisol and ACTH might be an indicator of the magnitude of surgical trauma, and also could be modulated by the use of analgesia techniques [23, 24].

As mentioned before, our study showed a tendency towards statistical significance in the relative change (T2–T0) in testosterone levels, with higher values observed in the ThPVB group, which could suggest that this method of analgesia might be more effective.

The review of the above cited studies confirmed the efficacy of aforementioned hormones and endogenous opiates in the evaluation of pain level. Although not statistically significant, the results of this study might be a part of the process of evaluating pain and stress markers as a measure of adequacy of perioperative analgesia regimens. It should be mentioned that oxycodone might have an influence on testosterone and cortisol levels (as a result of pharmacological interaction rather than its analgesic action). Adequate analgesia technique is of utmost importance during the perioperative period. The efficacy of the chosen method and its safety are equally important. Many studies have confirmed the safety of regional anaesthesia techniques, and thoracic paravertebral block is no exception. On the other hand, opiates, which are also very effective, may cause significant side effects (respiratory depression, hypotension, bradycardia, nausea, and vomiting). These may diminish the effects of physiotherapy and extend the recovery process.

Conclusions

Preoperative ThPVB is effective and safe for patients undergoing VATS. The use of balanced analgesia which consists of regional analgesia (ThPVB), non-opioid painkillers, and small doses of opioids can be an effective alternative for general anaesthesia using large doses of opioids. No statistically significant difference between 6 hours and 24 hours after surgery in the levels of hormones (testosterone, cortisol, α-amylase activity, sIgA, and β-endorphin) confirms the efficacy of analgesia consisting of ThPVB and low doses of opioids.

Trial registration

ClinicalTrials.gov as No. NCT04414488.

Author contributions

Study conception: S.B., M.S., H.M. Literature search: M.S., A.M., H.M. Data extraction: M.S., S.B., D.C. Statistics: S.B., M.S. Drafting manuscript: S.B., A.M., H.M. Finalising manuscript: all authors. Responsibility for the paper as a whole: S.B.

Funding and support

The work was financed by the Medical University of Silesia in Katowice: grant number: KNW-2-K01/N/8/N. The authors declare no conflict of interest.

Acknowledgements

The authors thank all participants in the study.

ORIGINAL PAPER

References

1. Bochenek A, Reicher M. Anatomia człowieka. Tom 2. PZWL Wydawnictwo Lekarskie, Warszawa 1965.
2. Wordliczek J, Dobrogowski J. Patofizjologia bólu pooperacyjnego. Przegl Lek. 2000; 57: 201–210.
3. Misiołek H, Zajączkowska R, Daszkiewicz A, et al. Postoperative pain management - 2018 consensus statement of the Section of Regional Anaesthesia and Pain Therapy of the Polish Society of Anaesthesiology and Intensive Therapy, the Polish Society of Regional Anaesthesia and Pain Therapy, the Polish Association for the Study of Pain and the National Consultant in Anaesthesiology and Intensive Therapy. Anaesthesiol Intensive Ther. 2018; 50(3): 173–199, doi: 10.5603/AIT.2018.0026, indexed in Pubmed: 30124229.
4. Long H, Tan Q, Luo Q, et al. Thoracoscopic Surgery Versus Thoracotomy for Lung Cancer: Short-Term Outcomes of a Randomized Trial. Ann Thorac Surg. 2018; 105(2): 386–392, doi: 10.1016/j.athoracsur.2017.08.045, indexed in Pubmed: 29198623.
5. Copik M, Bialka S, Daszkiewicz A, et al. Thoracic paravertebral block for postoperative pain management after renal surgery: A randomised controlled trial. Eur J Anaesthesiol. 2017; 34(9): 596–601, doi: 10.1097/EJA.0000000000000673, indexed in Pubmed: 28731925.
6. D'Ercole F, Arora H, Kumar PA. Paravertebral Block for Thoracic Surgery. J Cardiothorac Vasc Anesth. 2018; 32(2): 915–927, doi: 10.1053/j.jvca.2017.10.003, indexed in Pubmed: 29169795.
7. Sprouse-Blum AS, Smith G, Sugai D, et al. Understanding endorphins and their importance in pain management. Hawaii Med J. 2010; 69(3): 70–71, indexed in Pubmed: 20397507.
8. Elkhamisy E, Khalel M, Elbioumy A, et al. Beta-endorphin levels in both painful and painless diabetic peripheral neuropathy and its relations to pain characters and severity. Clin Diabetol. 2017; 6(5): 159–171, doi: 10.5603/dk.2017.0027.
9. Andrade Cde, Galvão-Moreira L, Oliveira Jde, et al. Salivary biomarkers for caries susceptibility and mental stress in individuals with facial pain. Cranio. 2019: 1–7, doi: 10.1080/08869634.2019.1607445, indexed in Pubmed: 31043147..
10. Stefaniak A, Kaczmarek U. Salivary α-Amylase and Cortisol as Stress Biomarkers — Literature Review. Dent Med Probl 2013; 50. ; 3: 271–274.
11. Afrisham R, Sadegh-Nejadi S, SoliemaniFar O, et al. Salivary Testosterone Levels Under Psychological Stress and Its Relationship with

Rumination and Five Personality Traits in Medical Students. Psychiatry Investig. 2016; 13(6): 637–643, doi: 10.4306/pi.2016.13.6.637, indexed in Pubmed: 27909455.
12. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain. 2015; 156(2): 280–288, doi: 10.1097/01.j.pain.0000460308.86819.aa, indexed in Pubmed: 25599449.
13. Terheggen MA, Wille F, Borel Rinkes IH, et al. Paravertebral blockade for minor breast surgery. Anesth Analg. 2002; 94(2): 355–9, table of contents, doi: 10.1097/00000539-200202000-00023, indexed in Pubmed: 11812698.
14. Hu Z, Liu D, Wang ZZ, et al. The efficacy of thoracic paravertebral block for thoracoscopic surgery: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018; 97(51): e13771, doi: 10.1097/MD.0000000000013771, indexed in Pubmed: 30572529.
15. Zhang W, Fang C, Li J, et al. Single-dose, bilateral paravertebral block plus intravenous sufentanil analgesia in patients with esophageal cancer undergoing combined thoracoscopic-laparoscopic esophagectomy: a safe and effective alternative. J Cardiothorac Vasc Anesth. 2014; 28(4): 966–972, doi: 10.1053/j.jvca.2013.12.007, indexed in Pubmed: 24686029.
16. Kaya FN, Turker G, Basagan-Mogol E, et al. Preoperative multiple-injection thoracic paravertebral blocks reduce postoperative pain and analgesic requirements after video-assisted thoracic surgery. J Cardiothorac Vasc Anesth. 2006; 20(5): 639–643, doi: 10.1053/j.jvca.2006.03.022, indexed in Pubmed: 17023279.
17. Casati A, Alessandrini P, Nuzzi M, et al. A prospective, randomized, blinded comparison between continuous thoracic paravertebral and epidural infusion of 0.2% ropivacaine after lung resection surgery. Eur J Anaesthesiol. 2006; 23(12): 999–1004, doi: 10.1017/S0265021506001104, indexed in Pubmed: 16824243.
18. Haager B, Schmid D, Eschbach J, et al. Regional versus systemic analgesia in video-assisted thoracoscopic lobectomy: a retrospective analysis. BMC Anesthesiol. 2019; 19(1): 183, doi: 10.1186/s12871-019-0851-2, indexed in Pubmed: 31623571.
19. Miecznikowski W, Kiczmer P, Seńkowska AP, et al. Comparison of two methods of cervical spine pain manual therapy using clinical and biochemical pain markers. Med Res J. 2019; 4(3): 163–170, doi: 10.5603/mrj.a2019.0034.
20. Chen ZY, Wang H, Xu W, et al. Effect of intravenous general anaesthesia with epidural block on the expression of pre-endogenous opioid peptide genes. J Int Med Res. 2014; 42(3): 765–772, doi: 10.1177/0300060513515642, indexed in Pubmed: 24743873.
21. Shirasaki S, Fujii H, Takahashi M, et al. Correlation between salivary alpha-amylase activity and pain scale in patients with chronic pain. Reg Anesth Pain Med. 2007; 32(2): 120–123, doi: 10.1016/j.rapm.2006.11.008, indexed in Pubmed: 17350522.
22. Yardeni IZ, Shavit Y, Bessler H, et al. Comparison of postoperative pain management techniques on endocrine response to surgery: a randomised controlled trial. Int J Surg. 2007; 5(4): 239–243, doi: 10.1016/j.ijsu.2006.09.008, indexed in Pubmed: 17660130.
23. Friedrich M, Rixecker D, Friedrich G. Evaluation of stress-related hormones after surgery. Clin Exp Obstet Gynecol. 1999; 26(2): 71–75, indexed in Pubmed: 10459440.
24. Harukuni I, Yamaguchi H, Sato S, et al. The comparison of epidural fentanyl, epidural lidocaine, and intravenous fentanyl in patients undergoing gastrectomy. Anesth Analg. 1995; 81(6): 1169–1174, doi: 10.1097/00000539-199512000-00009, indexed in Pubmed: 7486099.