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Original research paper

Effects of epidurally administered dexmedetomidine and dexamethasone on postoperative pain, analgesic requirements, inflammation, and oxidative stress in thoracic surgery

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ABSTRACT

The aim of this study was to compare the effects of dexmedetomidine and dexamethasone as adjuvants to preoperative epidural administration of local anesthetic (ropivacaine) in thoracic surgery on the postoperative level of pain, use of analgesics, inflammation, and oxidative stress. The study enrolled 42 patients who underwent elective thoracic surgery in a one-year period at the University Hospital Dubrava (Zagreb, Croatia). Based on a computer-generated randomization list the patients were assigned to the dexmedetomidine (n = 18) or dexamethasone (n = 24) group. Postoperatively, patients of dexmedetomidine group reported lower pain (VAS value 1 h post surgery, 3.4 ± 2.7 *vs.* 5.4 ± 1.8, dexmedetomidine *vs.* dexamethasone, $p < 0.01$) and had lower analgesic requirements in comparison with dexamethasone group. Thus, dexmedetomidine in comparison with dexamethasone was more efficient in lowering pain and analgesia requirements 24 h after the surgery. On the contrary, dexamethasone had better anti-inflammatory properties (CRP level 24 h post surgery, 131.9 ± 90.7 *vs.* 26.0 ± 55.2 mg L^{-1}, dexmedetomidine *vs.* dexamethasone, $p < 0.01$). Both dexmedetomidine and dexamethasone exhibited antioxidant effects, however, their antioxidant properties should be further explored. The results of this study improve current knowledge of pain control in thoracic surgery.

Keywords: dexmedetomidine, dexamethasone, thoracotomy, local anesthetic, analgesic efficacy

Every surgical procedure is inevitably accompanied by a stress response in the patient's organism, which encompasses inflammatory, metabolic, hormonal, and genomic disturbances (1). Although physiological, surgical stress can have detrimental consequences on convalescence, various organ functions, and overall morbidity (2). Oxidative stress, a state of imbalance between reactive oxygen (ROS) and nitrogen species (RNS) production,

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and the organism's detoxifying mechanisms, is a part of this process (3). Oxidative stress is associated with complications such as sepsis, liver failure, myocardial injury, kidney failure, pulmonary edema, and an increase in mortality rate (4).

The extent of perioperative stress is largely dependent on the severity of surgical injury, especially since it is well-known that pain plays an important role in surgical stress response maintenance (2). Thoracotomy, an integral part of thoracic surgery, is one of the most painful surgical procedures, where incision, muscle and ligament manipulations, rib retraction and fractures, irritation of the pleura, and intercostal nerve stretching all contribute to pain intensity (5). Also, thoracic procedures commonly require one-lung ventilation (OLV) which, together with subsequent re-expansion of atelectatic lung, amplifies stress due to free radical generation and can consequently boost aforementioned system impairments (6). Nowadays, placing a thoracic epidural catheter is one of the most successful approaches in pain management, and therefore is considered the "gold standard" of pain control in thoracic surgery (7). Agents commonly infused *via* epidural catheter include local anesthetics and/or opioids, and the choice is based on the patient's individual characteristics (8).

Dexmedetomidine is a highly selective short-acting agonist of α_2 adrenergic receptors which found its place in anesthesia practice as it produces analgesia, anxiolysis, and sedation without causing respiratory depression. Other advantages of its use include hemodynamic stabilization, sympatholytic effect, organ protection, and anti-inflammatory action (9–13). A recent meta-analysis showed that perioperative use of dexmedetomidine attenuates stress response, blood epinephrine, norepinephrine, cortisol, and blood glucose in surgical patients (12, 13). Dexmedetomidine also decreased the pro-inflammatory cytokines in various conditions including cardiopulmonary bypass, severe sepsis, and surgery which is explained by its attenuation of the hypothalamic-pituitary-adrenal axis (13). Results from the randomized controlled studies suggest that the anti-inflammatory effect of dexmedetomidine has the potential to improve surgical patients' outcomes, but to date, there is not enough evidence for long-term outcomes (11). When applied epidurally dexmedetomidine prolongs both sensory and motor blockade induced by local anesthetic, as it is rapidly absorbed into the cerebrospinal fluid where it binds to its target receptors located in the spinal cord (14). Clinical trials confirm dexmedetomidine's place in thoracic epidural analgesia. Zeng *et al.* compared the effects of intravenous (*i.v.*) and epidurally administrated dexmedetomidine in patients undergoing open thoracotomy and showed that epidurally applied dexmedetomidine provides better analgesia and inhibits the cardiovascular response after intubation and extubation (15). The addition of dexmedetomidine (0.5 μg kg^{-1}) to bupivacaine in ultrasound-guided erector spinae plane block (ESPB) enhanced analgesia in open thoracotomy (16). Additionally, Agamohammdi *et al.* showed that, in patients with multiple rib fractures, adding dexmedetomidine to bupivacaine epidural infusion provides better pain control than bupivacaine alone (17). Furthermore, Cekic *et al.* induced pneumoperitoneum in rats, an oxidative stress state, and found that the application of dexmedetomidine reduces the oxidative stress index (18). In the OLV setting, Gao *et al.* showed that preoperative *i.v.* injection of dexmedetomidine (1 μg kg^{-1}) induces the expression of heme oxygenase-1 in lung tissue, a protective protein in the stress reaction, suggesting a pathway by which dexmedetomidine could reduce oxidative stress and inflammation, consequently protecting from lung injury (19). Although the aforementioned results seem to favor dexmedetomidine as a safe agent for epidural anesthesia and show its antioxidant effect, to our knowledge no study investigated its direct effect on oxidative stress in thoracic epidural anesthesia. Bulk of dexmedetomidine

studies still focus mostly on its *i.v.* applications and its perioperative epidural application is mentioned only in terms of anesthetic sparing and enhancement of analgesia (19). Yu *et al*. in their systemic review and meta-analysis showed that dexmedetomidine dose-dependently prolongs postoperative analgesia duration (20). All of this indicates that dexmedetomidine may benefit surgical patients during the perioperative period and may improve the clinical outcomes of surgical patients (12).

On the other hand, dexamethasone is a long-acting, high-potency steroid, well-known and widely used in clinical practice for its powerful and effective anti-inflammatory properties (21). Its epidural application has an opioid-sparing analgesic effect and may improve postoperative outcomes in terms of better pain control (22, 23). Further on, Khafagy *et al*. showed that epidural bupivacaine-dexamethasone admixture has similar analgesic potency as bupivacaine-fentanyl with opioid-sparing and antiemetic effects (24). Thomas and Beevi administrated preoperatively dexamethasone (5 mg) epidurally to patients undergoing laparoscopic cholecystectomy and found that, with or without bupivacaine, it reduces postoperative pain and the need for morphine application (25). Hefni *et al*. compared different doses of epidural dexamethasone and found that a higher dose (8 mg) provides superior analgesia compared to lower doses (4 and 6 mg) without increasing glucose levels or delaying wound healing (26). Also, a study by Razavizadeh *et al*. showed that adding dexamethasone to bupivacaine significantly prolongs the duration of postoperative analgesia (27).

Although the analgesic effect of both drugs is proven, their antioxidant properties are merely suggested, mostly in animal models (28–32). Until now, no study compared the effects of dexmedetomidine and dexamethasone as adjuvants to preoperative epidural administration of local anesthetic on postoperative pain, analgesic requirements, the level of inflammation, and oxidative stress in thoracic surgery. Hence, the aim of this study was to compare the effects of dexmedetomidine and dexamethasone as local anesthetic adjuvants in patients undergoing thoracic surgery on postoperative levels of pain, analgesic requirements, inflammation, and oxidative stress levels. This study included patients undergoing thoracic surgery who received either dexmedetomidine or dexamethasone as an adjuvant to ropivacaine, administered into thoracic epidural space. After the surgery, the patients were monitored for their pain score and analgesic requirements. Additionally, in blood samples collected prior to local anesthesia and at several time points in 24 h postoperatively, routine laboratory tests, including parameters of inflammation were evaluated. Moreover, in collected blood samples biomarkers of oxidative stress, glutathione (GSH), superoxide dismutase (SOD), as biomarkers of antioxidant defense, and malondialdehyde (MDA) and protein carbonyls (PC) as biomarkers of oxidative damage were measured. The results of this study will improve knowledge of pain control in thoracic surgery.

EXPERIMENTAL

Patients

42 patients who underwent elective thoracic surgery in the period from February 2019 to February 2020 (the period of a year) in the University Hospital Dubrava (Zagreb, Croatia) were enrolled in the study.

The investigation was conducted after approval of the Ethics Committee of the University Hospital Dubrava (Zagreb, Croatia) and observed the ethical principles of the Declaration

of Helsinki. All study participants signed informed consent. The investigation was registered on ClinicalTrials.gov (NCT03632460). Exclusion criteria were patients with a history of neurologic and/or psychiatric disease, myocardial ischemia, corticosteroid therapy, severe valve stenosis, liver or renal insufficiency, drug allergies, hemostatic disorders, non-compliant patients, and duration of surgery procedure longer than six hours.

Study design

All patients required thoracotomy and OLV. Prior to the surgery, the patients received no pre-medication (anxiolytic or analgesic pre-medication) in order to minimize confounding bias on perioperative pain level. The epidural catheter was placed using a percutaneous approach to the thoracic epidural space using needle puncture, placed at Th7/Th8 level, guided by surface anatomic landmarks. Preoperatively, *i.v.* access was obtained, oxygen was administered, and routine monitoring was set.

According to a computer-generated randomization list, patients were randomly assigned to two groups. A randomization schedule was computer-generated by a biostatistician (not otherwise involved in the study). The anesthesiologist in charge throughout the operation was aware of group allocation and was not involved in postoperative management and data collection. All patients, anesthesiologists, and personnel involved in the patient management and data collection were unaware of the group to which the patient had been allocated.

Prior to general anesthesia, the first group (dexmedetomidine group) received epidurally a slow bolus of 0.375 % ropivacaine (8 mL) augmented with 1.0 μg kg^{-1} dexmedetomidine (Deksmedetomidin®, Pliva, Croatia) while to the second group (dexamethasone group) adjuvant to an epidural slow bolus of 0.375 % ropivacaine (8 mL) was 8 mg of dexamethasone (Dexamethasone®, Krka, Slovenia). To facilitate endotracheal intubation general anesthesia was induced with fentanyl (2–3 μg kg^{-1}), propofol (2–3 mg kg^{-1}), and rocuronium (0.6 mg kg^{-1}). The general anesthesia was maintained using sevoflurane, nitrous oxide (50 % in oxygen), boluses of fentanyl, and rocuronium. A double-lumen endotracheal tube was inserted after the rocuronium injection and connected to an anesthesia apparatus for mechanical ventilation. The proper tube position was confirmed by auscultation and fiberoptic bronchoscopy. The ventilation settings during surgery were tidal volume (7–10 mL kg^{-1} $_{\text{(ideal body weight)}}$), a fraction of inspired oxygen (0.5–1.0), and end-tidal CO_2 partial pressure (35–45 mmHg). Following surgery, patients were admitted to the Intensive Care Unit (ICU).

Prior to the surgical procedure and during the surgical procedure, heart rate (HR), mean arterial pressure (MAP), electrocardiogram (ECG), oxygen saturation, and fluid volume were continuously monitored. HR and MAP were continuously monitored for the next 24 h postoperatively and were recorded at 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after the surgical procedure.

Pain score and analgesic consumption

For the next 24 h, while patients were at ICU, pain scores and consumption of analgesics were monitored and recorded at 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after the surgery.

Pain score was determined using the visual analog scale (VAS) for pain assessment. The VAS provides a simple, efficient, and minimally intrusive measure of pain intensity that has been used widely in research settings when a quick index of pain is required. It consists of a 10 cm horizontal line with the two endpoints labeled "no pain" and "worst possible pain" (that correlates the scale from 0 to 10 cm/0 to 10). The patients are requested to mark the point that relates to the present level of pain intensity. The distance in centimeters from the low end of the scale and the patient's mark is used as the numerical index of pain intensity.

If the patients required pain treatment (VAS > 4) morphine (10 mg in 20 mL of saline) was given epidurally, and non-steroidal anti-inflammatory drugs (NSAID) ketoprofen (100 mg) or paracetamol (1.0 g) *i.v.* were applied as needed. The time and the type of analgesic were recorded for the first 24 h postoperatively.

Blood sampling

Prior to an epidural application (T0, baseline value), and 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after the surgery venous blood samples were collected according to the hospital (University Hospital Dubrava) protocol for routine laboratory tests: hemoglobin level (Hb), leukocyte count (WBC), urea, creatinine, and C-reactive protein (CRP) level.

The venous blood samples for assessment of oxidative stress parameters were collected prior to epidural application (T0, baseline value), 1 h after the beginning of the surgical procedure (t1), and 2 h (t2) after the surgery on vacutainers containing EDTA as an anticoagulant. EDTA was used as an anticoagulant since EDTA, by chelating iron that is necessary for superoxide-driven Fenton reaction, prevents oxidative stress *in vitro* (33).

Laboratory tests

Collected samples of venous blood at T0, T1, T2, T3 and T4 underwent routine laboratory tests using biochemical tests procured from Simens Healthcare Diagnostic (Simens HD, Germany) on automated analyzer Olympus AU 400 (Olympus, Japan). Leukocyte count was measured on an automated Bechman Coulter HIX flow cytometer (Bechman Coulter, USA).

Oxidative stress parameter GSH was determined according to Ellman's method as described in Duka *et al*., MDA (a biomarker of lipid peroxidation) according to Domijan *et al*., and the method for assessment of PC (biomarker of oxidatively modified proteins) was based on Dalle-Donne *et al*. (34–36). The SOD activity in plasma samples was determined by the use of a commercial kit (Cayman Chemicals, USA) and the assay was performed according to the manufacturer's instructions. All measurements were performed on a UV-Vis spectrophotometer (PG Instruments, UK) or on a microplate reader (Spectra i3x, Molecular Devices, USA).

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical data as counts and percentages.

The normality of distribution was tested using the Shapiro-Wilk test. Differences in categorical variables were tested using χ^2 tests. Student's *t*-test or Mann-Whitney U test

were used to test the difference in continuous variables between groups, according to distribution.

Differences in repeated measurements between groups for continuous variables were tested using the Wilcoxon test for paired samples for 2 measurements or two-way repeated measurement analysis of variance (RM-ANOVA) with between and within group interactions and post hoc Holm-Sidak correction for 3 or more measurements. When data were non-normal distributed, statistical significance for repeated measurements was tested using Friedman's test.

Statistical analysis was performed using Jamovi v1.1.7. $p \leq 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

Study group

In this study, patients who underwent thoracic surgery, received either dexmedetomidine or dexamethasone as adjuvants to thoracic epidural local anesthetic (ropivacaine) prior to general anesthesia, and postoperative level of pain, use of analgesics, inflammation and oxidative stress parameters were followed.

In total 42 patients participated in the study. The mean age of enrolled patients was 68.3 ± 11.3 years and there were 31 (74 %) males and 11 (26 %) females. Prior to the surgical procedure the patients were classified according to the American Society of Anesthesiologists (ASA) physical status classification system. According to the ASA, preoperative classification ASA I patient is a normal healthy patient, ASA II has mild systemic disease, and ASA III patient has severe systemic disease that limits her/his activity but is not incapacitating. Based on the ASA classification, 2 patients (5 %) were ASA I, 17 patients (40 %) were ASA II and 23 patients (55 %) were ASA III. 7 patients (17 %) were operated on for esophageal cancer, 28 (67 %) for lung cancer, 2 (5 %) for pleural mesothelioma, and 5 patients (12 %) were diagnosed with other, non-malignant diseases.

Based on the computer-generated randomization, 42 patients were divided into two groups, 18 patients were allocated to the dexmedetomidine group (prior to general anesthesia as adjuvant to epidural ropivacaine dexmedetomidine (1.0 μg kg^{-1}) was used) and 24 patients to dexamethasone group (as adjuvant to ropivacaine dexamethasone (8.0 mg) instead of dexmedetomidine was applied).

Prior to epidural application (baseline value, T0) there was no significant difference between dexmedetomidine and dexamethasone groups regarding HR, MAP, laboratory test values (Hb, urea, creatinine), inflammation (WBC and CRP), and oxidative stress parameters (Table I and Table V). No complications or adverse events were reported during surgery and the perioperative period.

In the 24-hour postoperative period, in both groups HR increased, however, the increase was significant only in the dexmedetomidine group ($p < 0.01$; Table II). MAP decreased in both groups, but a significant decrease was only observed in the dexamethasone group ($p < 0.01$; Table II). No difference in HR and MAP between dexmedetomidine and dexamethasone groups was observed (Table II). In their randomized controlled study Agarwal *et al*. showed that dexmedetomidine can reduce the increase of MAP and HR during intubation and extubation, however, more patients suffered bradycardia and

hypotension (37). It is reported that a high concentration of dexmedetomidine load can result in hypotension or bradycardia (38). Therefore, the dosage and the mode of administration of dexmedetomidine should be strictly controlled. In thoracic surgery, dexmedetomidine may offer several physiologic benefits. It reduces the sympathetic response to a surgical stimulus which may provide cardio-protective benefits.

The level of urea and creatinine was in the referent range (ref. range for urea: 2.8–8.3 mmol L^{-1}; ref. range for creatinine: 49–104 μmol L^{-1}) and there was no significant difference

Table I. Characteristics of patients (n = *42) at the beginning of the study (baseline values; prior to epidural application of local anesthetic). Patients were randomly (computer-generated) allocated into dexmedetomidine (DM;* n = *18) and dexamethasone (DX;* n = *24) group*

	DM	DX	*p*
Gender			
Female	4 (36 %)	7 (64 %)	0.61
Male	14 (45 %)	17 (55 %)	
Age	65.6 ± 7.1	62.5 ± 13.6	0.52
ASA			
I	0	2 (100 %)	0.03
II	4 (24 %)	13 (76 %)	
III	14 (61 %)	9 (39 %)	
Diagnosis			
Lung cancer	13 (46 %)	15 (54 %)	0.85
Esophageal cancer	2 (29 %)	5 (71 %)	
Mesothelioma	1 (50 %)	1 (50 %)	
Other	2 (40 %)	3 (60 %)	
Lab tests			
Hb (g L^{-1})	134.4 ± 15.8	139.9 ± 14.3	0.25
WBC (×10^9 L^{-1})	8.7 ± 2.4	7.8 ± 2.5	0.27
Urea (mmol L^{-1})	7.7 ± 6.9	5.9 ± 2.5	0.50
Creatinine (mol L^{-1})	92.2 ± 53.5	80.1 ± 27.4	0.76
CRP (mg L^{-1})	19.8 ± 29.4	9.9 ± 12.3	0.46
Hemodynamic parameters			
HR (bpm)	77.1 ± 15.9	78.7 ± 16.3	0.76
MAP (mmHg)	97.1 ± 10.1	104.9 ± 15.6	0.08

Hb – hemoglobin; WBC – leukocyte count; CRP – C reactive protein; HR – heart rate; MAP – mean arterial pressure. Results are presented as mean ± SD for continuous variables, counts, and percentages for categorical variables.

in the level of urea and creatinine within the group and between groups in 24 h postoperative period (Table III). Prior to the surgery, the level of Hb was in the ref. range (119–157 g L^{-1}). In the 24 h period after the surgery, Hb level decreased in both groups ($p < 0.01$; Table III) and we attributed this to blood loss (chest drainage) and hemodilution due to *i.v.* fluid (crystalloid and/or colloid) administration. Two hours after the surgery, the Hb level in the dexmedetomidine group was significantly lower than in the dexamethasone group ($p = 0.02$; Table III). However, the decrease in the level of Hb is of no clinical significance, since in both groups the level of Hb was well above transfusion triggers and no blood transfusion was needed.

Impact of dexmedetomidine and dexamethasone on postoperative pain and analgesic requirements after the surgery

The level of postoperative pain was scored as VAS. VAS is a simple way to assess pain intensity and it has been widely used in research settings. The level of pain is scored as

Table II. Changes in heart rate (HR), mean arterial pressure (MAP), and visual analog scale (VAS) as a measure of pain in dexmedetomidine (DM; n *= 18) and dexamethasone (DX;* n *= 24) groups prior to epidural application of local anesthetic and at different time points after the surgery*

	DM	DX	p_w	p_b
HR				
T0	77.1 ± 15.9	78.7 ± 16.3	DX	
T1	70.1 ± 19.3	82.8 ± 12.8	0.22	
T2	77.1 ± 15.0	84.4 ± 13.9		0.42
T3	79.1 ± 11.9	78.4 ± 19.7	DM	
T4	86.4 ± 15.1	81.9 ± 13.4	< 0.01	
MAP				
T0	97.1 ± 10.1	104.9 ± 15.6	DX	
T1	93.2 ± 13.5	102.2 ± 13.6	< 0.01	
T2	92.5 ± 9.0	91.3 ± 13.6		0.66
T3	92.6 ± 10.8	88.4 ± 15.2	DM	
T4	95.9 ± 11.9	93.8 ± 12.6	0.44	
VAS				
T0	1.2 ± 0.5	1.4 ± 0.4	DX	
T1	3.4 ± 2.7	5.4 ± 1.8	< 0.01	
T2	3.3 ± 2.7	4.0 ± 2.2		0.01
T3	2.3 ± 1.5	3.2 ± 2.1	DM	
T4	1.9 ± 1.5	2.5 ± 1.4	0.016	

T0 – prior to epidural application of local anesthetic, baseline value; T1 – 1 h after the surgery; T2 – 6 h after the surgery; T3 – 12 h after the surgery; T4 – 24 h after the surgery. The difference within each group (p_w) and between (p_b) groups was tested by RM ANOVA; post hoc Holm-Sidak correction was applied for HR and MAP, Friedman's test for VAS.

Table III. Laboratory parameters hemoglobin (Hb), leukocyte count (WBC), urea, creatinine, and C-reactive protein (CRP) in dexmedetomidine (DM; n *= 18) and dexamethasone (DX;* n *= 24) group prior to epidural application of local anesthetic and at different time points after the surgery*

	DM	DX	p_w	p_b
Hb (g L^{-1})				
T0	134.4 ± 15.8	139.9 ± 14.3	DX	
T1	108.4 ± 18.9	122.64 ± 17.3	< 0.01	
T2	114.0 ± 16.1	121.7 ± 13.1		0.02
T3	118.1 ± 11.2	115.1 ± 12.9	DM	
T4	110.1 13.3	113.8 ± 10.4	< 0.01	
WBC (×10^9 L^{-1})				
T0	8.7 ± 2.4	7.8 ± 2.5	DX	
T1	9.9 ± 3.4	11.4 ± 4.8	< 0.01	
T2	12.1 ± 4.3	12.2 ± 4.3		0.71
T3	12.0 ± 3.8	11.5 ± 4.1	DM	
T4	10.4 ± 2.4	11.6 ± 3.1	< 0.01	
Urea (mmol L^{-1})				
T0	7.7 ± 6.9	5.9 ± 2.5	DX	
T1	7.2 ± 7.2	5.3 ± 1.6	0.42	
T2	6.0 ± 1.4	5.8 ± 1.5		NS
T3	9.0 ± 8.5	7.1 ± 2.4	DM	
T4	5.5 ± 2.7	5.9 ± 1.7	0.22	
Creatinine (μmol L^{-1})				
T0	92.2 ± 53.5	80.1 ± 27.4	DX	
T1	77.9 ± 54.5	58.5 ± 18.5	0.17	
T2	75.0 ± 6.8	69.8 ± 11.8		
T3	85.8 ± 69.0	73.5 ± 3.5	DM	NS
T4	66.6 ± 21.4	70 ± 13.1	0.21	
CRP (mg L^{-1})				
T0	19.8 ± 29.4	9.9 ± 12.3	DX 0.2	< 0.01
T4	131.9 ± 90.7	26.0 ± 55.2	DM < 0.01	

T0 – prior to epidural application of local anesthetic, baseline value; T1 – 1 h after the surgery; T2 – 6 h after the surgery; T3 – 12 h after the surgery, T4 – 24 h after the surgery; NS – not significant. Within (p_w) and between (p_b) groups difference was tested by RM ANOVA; post hoc Holm-Sidak correction was applied for Hb and WBC, and Friedman's test for urea and creatinine. The difference in CRP was tested by the Mann-Whitney U test, and for CRP paired samples after 24 h Wilcoxon test was applied.

VAS in the range from 0–10 (0 to 10 cm). In both groups, we recorded the highest VAS 1 h after the surgery ($p < 0.02$; Table II), however in the dexamethasone group, VAS was higher in comparison with the dexmedetomidine group ($p < 0.01$; Table II). In the dexmedetomidine group, VAS was less pronounced and had a tendency to return to baseline value 24 h after the surgery (Table II). These results clearly indicate that dexmedetomidine as an adjuvant to epidural ropivacaine prior to general anesthesia reduces postoperative pain more efficiently.

Results on analgesic requirements of both groups after the surgery (1 h till 24 h after the surgery) are presented in Table IV. 12 h after the surgery a significant difference in analgesic requirements between groups was observed ($p = 0.02$; Table IV). In the dexmedetomidine group, 89 % of patients had no need for analgesics, and 11 % were administered ketoprofen *i.v.* and none were administered epidural morphine. In the dexamethasone group, 50 % of patients had no need for analgesics, and 25 % were administered ketoprofen *i.v.* and 25 % of patients were administered epidural morphine (Table IV). At other time points, there was no difference in analgesic requirements between groups. Lower requirements of analgesic postoperatively confirm that dexmedetomidine ensures less pain after the surgery. Our results suggest that compared with dexamethasone, adding

Table IV. The analgesic requirements of the patients in dexmedetomidine (DM; n *= 18) and dexamethasone (DX;* n *= 24) groups 1, 6, 12, and 24 h after surgery*

	DM	DX	*p*
1 h			
None	10 (56 %)	5 (21 %)	
NSAID *i.v.*	3 (17 %)	5 (21 %)	0.06
Morphine epidural	5 (28 %)	14 (58 %)	
6 h			
None	11 (61 %)	14 (58 %)	
NSAID *i.v.*	5 (28 %)	5 (21 %)	0.67
Morphine epidural	2 (11 %)	5 (21 %)	
12 h			
None	16 (89 %)	12 (50 %)	
NSAID *i.v.*	2 (11 %)	6 (25 %)	0.02
Morphine epidural	0 (0 %)	6 (25 %)	
24 h			
None	14 (78 %)	18 (75 %)	
NSAID *i.v.*	4 (22 %)	4 (17 %)	0.43
Morphine epidural	0 (2 %)	0 (8 %)	

NSAID – non-steroid anti-inflammatory drug; *i.v.* – intravenously. Data are presented as percentages. Statistical analysis of data was performed by the use of χ^2 test.

dexmedetomidine to ropivacaine elevates the nociceptive threshold in patients undergoing thoracotomy, thus lowering pain and the postoperative analgesic requirements.

It is important to emphasize that in our study no anxiolytic or analgesic pre-medication was administered prior to the surgery in order to minimize confounding bias on perioperative pain level. The mechanism of dexmedetomidine analgesia has not been fully clarified, but the main mechanisms might be due to peripheral analgesic effect, central analgesic effect, and local analgesic effect (modulation of hyperalgesia by stimulating the α_2 receptor) (38). Previously, Agamohammid *et al*. observed that dexmedetomidine added to bupivacaine epidural infusion provides better pain control than bupivacaine alone (22). Hamed *et al*. showed that adding dexmedetomidine in ultrasound-guided ESPB is associated with a better analgesic effect by reducing intraoperative fentanyl and postoperative morphine consumption with a more prolonged analgesic effect and stable hemodynamics (39). Also, Song and Lu in a meta-analysis of randomized controlled trials reported that dexmedetomidine administered before anesthesia in thoracoscopic surgery can substantially improve the analgesic efficacy (40). The study in which dexmedetomidine and dexamethasone were compared in prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy (the patients received either single dose of dexmedetomidine or dexamethasone before skin incision) demonstrated that the patients in dexmedetomidine group had lower severity of pain, higher sedation score, requested the first analgesic postoperatively later, and the amount of postoperative administrated tramadol was lower (41). Similarly, in the study in which dexmedetomidine and dexamethasone were compared as adjuvants to bupivacaine analgesia in preperitoneal post-cesarean section lower pain scores, prolonged time to first analgesic request was observed in dexmedetomidine group (42).

Impact of dexmedetomidine and dexamethasone on the level of inflammation and oxidative stress after the surgery

In this study, we used WBC and CRP as inflammatory parameters. Regarding WBC, 1, 6, 12, and 24 h after the surgery, we recorded a steady increase in both, dexmedetomidine and dexamethasone groups ($p < 0.01$), and we observed no difference between the groups ($p = 0.71$; Table III). In both groups 24 h after the surgery we recorded an increase in CRP level in comparison to the baseline value (T0), however, the increase in CRP level was only significant in the dexmedetomidine group ($p < 0.01$; Table III). The difference between groups was observed ($p < 0.01$; Table III) indicating that dexamethasone has a better anti-inflammatory effect. The anti-inflammatory property of dexamethasone is well known (21, 22). Literature data demonstrates that dexmedetomidine can decrease inflammation (9, 10). In the study in which dexmedetomidine was used as an anesthetic adjuvant in patients undergoing myocardial surgery under mini-cardiopulmonary bypass, a lower level of inflammatory parameters was recorded in a group that together to conventional anesthesia received dexmedetomidine in comparison to the group of patients that received just conventional anesthesia (43). According to the literature, both dexmedetomidine and dexamethasone have anti-inflammatory properties. However, in our study dexamethasone reduced inflammation more effectively.

Due to the fast absorption of dexmedetomidine and since we wanted to capture the early effect of dexmedetomidine and dexamethasone on oxidative stress, blood samples for assessment of parameters of oxidative stress were collected prior to epidural application (baseline value, T0), one hour (t1) after the beginning of the surgery and two hours (t2) after the surgery. In general, all parameters of oxidative stress were higher before surgery.

All the parameters of oxidative stress decreased 2 h after the surgery (2 h postoperatively) (Table V). From the assessed parameters, the most significant decrease was observed for the GSH level. GSH, a small molecular tripeptide, is the most important antioxidant and detoxifying compound in the organism (34, 44). Its level decreases in the state of oxidative stress, however, to cope with oxidative stress cells can synthesize GSH *de novo* (44). We observed the decrease in GSH levels in both groups already 1 h after the beginning of surgery ($p < 0.03$; Table V). The decrease was more pronounced in the dexmedetomidine group, but the difference between the groups was not significant ($p = 0.56$; Table V). Except

Table V. Oxidative stress parameters superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA), and protein carbonyls (PC) in dexmedetomidine (DM; n *= 18) and dexamethasone (DX;* n *= 24) group prior to epidural application of local anesthetic and at different time points during and after the surgery*

	DM	DX	p_w	p_b
SOD (U mL^{-1})				
Baseline (T0)	1.6 ± 0.7	1.5 ± 0.7	DX	
1 h after the incision (t1)	1.9 ± 1.2	1.3 ± 0.8	0.23	
				0.2
2 h post surg. (t2)	1.5 ± 0.8	1.2 ± 0.6	DM	
			0.12	
GSH (μmol L^{-1})				
Baseline (T0)	25.3 ± 18.4	25.7 ± 20.8	DX	
1 h after the incision (t1)	20.4 ± 18.6	21.6 ± 15.9	0.03	
				0.56
2 h post surg. (t2)	12.4 ± 4.4	13.3 ± 6.0	DM	
			< 0.01	
MDA (μmol L^{-1})				
Baseline (T0)	5.8 ± 2.3	5.2 ± 3.0	DX	
1 h after the incision (t1)	4.4 ± 1.9	5.2 ± 3.2	0.03	
				0.63
2 h post surg. (t2)	4.4 ± 2.2	4.2 ±1.6	DM	
			< 0.01	
PC (μmol L^{-1})				
Baseline (T0)	16.1 ± 3.0	17.7 ± 5.0	DX	
1 h after the incision (t1)	16.5 ± 2.5	16.3 ± 4.1	0.14	
				0.48
2 h post surg. (t2)	13.9 ± 2.8	15.7 ± 3.9	DM	
			0.19	

T0 – prior to epidural application of local anesthetic, baseline value; t1 – 1 h after the beginning of the surgery/1 h after the incision; t2 – 2 h after the surgery. The difference within (p_w) and between (p_b) the groups was tested with RM ANOVA, and post hoc Holm-Sidak correction was applied.

for GSH as an antioxidant, we monitored SOD. Within the cell, SOD captures free radicals, in particular, superoxide anion, and converts it to less harmful hydrogen peroxide (45). Although in the time course followed (2 h postoperatively) a decrease in SOD levels was observed, the decrease was not significant within the group and also the difference between the groups was not observed (Table V).

We further assessed MDA and PC as parameters of oxidative damage of macromolecules. MDA is a biomarker of oxidative damage of lipids (in particular cell membrane lipids), while PC is a biomarker of oxidative modification of proteins (35, 36). In both groups, 2 h after the surgery, the level of MDA and PC decreased in comparison to the baseline value (prior to epidural application of either dexmedetomidine or dexamethasone as adjuvants to local anesthetic). For MDA this decrease was significant ($p < 0.03$, Table V). We observed no difference between groups but in the dexmedetomidine group, the level of MDA decreased already 1 h after the beginning of surgery. These results indicate that 2 h after the surgery the level of oxidative stress decreased.

Results of this study suggest that both dexmedetomidine and dexamethasone decrease oxidative stress parameters. Surgery of any kind and anesthesia are connected to increased oxidative stress (3, 6). In a previous study, Bulow *et al*. found an increase in oxidative stress parameter MDA 24 h after the coronary arterial bypass graft surgery under mini-cardiopulmonary bypass (43). However, in that study, the level of MDA was assessed in erythrocytes, not in plasma. On the other hand, in the study that compared *i.v.* infusion of dexmedetomidine and midazolam in dental implantation, lower oxidative stress was found in the dexmedetomidine group in comparison to the midazolam group (46). Also, Kim *et al*. showed that intraoperative dexmedetomidine administration reduces stress responses in patients undergoing major spinal surgery (13). Thus, our study confirms that dexmedetomidine as well as dexamethasone can lower oxidative stress. Therefore, their antioxidant property should be further explored.

There are certain weaknesses of this study. The study included a relatively low number of patients. Although lung cancer still has a relatively high incidence compared to other tumors, certain therapies such as lesion-targeted radiotherapy have gained traction in recent years and caused a reduction in the number of surgically treated patients. Another cause for a relatively low number of patients is the fact that not all patients undergoing thoracotomy will receive thoracic epidural anesthesia due to various reasons (difficult anatomy or organizational difficulties). However, even with this shortcoming, certain conclusions can be drawn, and the results close to statistical significance should be further investigated in multicentric studies. Also, a difference between the frequency of ASA classification grade II and III patients between groups was detected, however, there was no significant difference in baseline values (T0) of vital parameters that may be affected by patients' ASA classification – HR or MAP (since many patients with higher ASA classification status have moderate to severe cardiovascular comorbidities such as coronary artery disease, atrial fibrillation, and valvular defects). Additionally, according to a study by Schick *et al*., ASA status does not affect the nociceptive threshold and should not be considered a confounding factor when interpreting the results (47).

CONCLUSIONS

This is the first study that compared the effects of dexmedetomidine and dexamethasone as adjuvants to local anesthetic in thoracic surgery on the postoperative level of pain,

use of analgesics, inflammation, and oxidative stress level. Results of this study indicate that dexmedetomidine, when applied as an adjuvant to local anesthetic, reduces postoperative pain more effectively resulting in lower postoperative analgesic requirements. On the other hand, dexamethasone demonstrated a better anti-inflammatory effect, however further longitudinal analyses are needed to determine the long-term benefit of dexamethasone over dexmedetomidine on inflammation. Additionally, both dexmedetomidine and dexamethasone reduced the level of oxidative stress, however, no difference in the reduction of oxidative stress between groups was observed. Therefore, the antioxidant effect of dexmedetomidine and dexamethasone should be further explored.

Conflict of interest. – The authors declare no conflict of interest.

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