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Open Lobectomies and Cardiac Biomarkers

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ABSTRACT

OBJECTIVE: Troponin is a sensitive biomarker for cardiovascular injury. In lobectomies, perioperative analgesia can be performed with either a combination of thoracic epidural anesthesia and general anesthesia or general anesthesia alone. We wish to demonstrate that patients who receive the former tend to have lower levels of troponin.

METHOD: In this prospective observational study, we included patients who underwent open lobectomy. Cardiovascular markers were recorded postoperatively, in order to correlate the fluctuation of these markers with the application or not of thoracic epidural anesthesia.

RESULTS: Forty eight (48) patients were enrolled, 15 (31.3%) received a combination of thoracic epidural anesthesia with general anesthesia, while 33 (68.7%) received general anesthesia alone. Patients with epidural anesthesia were found to have significantly lower levels of troponin 12-24 hours after surgery (8.9±4.1 versus 16.8±10.5, $p < 0.05$), while 48 to 72 hours postoperatively, the troponin values of the two groups did not appear to differ (10.7±6.9 vs. 14.8±8.3, p 0.103). Age, sex and body mass index were not found to be significantly associated with the fluctuation of troponin values in this setting.

CONCLUSION: Patients who undergo open lobectomy receiving a combination of general and thoracic epidural anesthesia appear to maintain lower troponin levels in the immediate postoperative period than patients receiving general anesthesia alone.

KEY WORDS: *combined thoracic epidural anesthesia, thoracotomy, troponin, lobectomy*

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INTRODUCTION

It is estimated that 234 million people require inpatient surgery every year. The rate of serious complications resulting in permanent disability or death, varies from 0,4 to 0,8 % i.e. 2 million per year in the developed world[1]. Troponin is a cardiac biomarker that is used primarily to diagnose myocardial infarction (MI). However, it is also released in various conditions such as acute pulmonary embolism, heart failure, or end stage renal disease[2].

A significant association between postoperative troponin levels and 30- day mor-

Limitations: The relatively small sample of patients participating in the study demonstrates the need for further research to reach safe conclusions.

Conflict of Interest: none declared

tality has been reported. A significant association between short-term postoperative (up to 72h) peak troponin and 30-day mortality has been found, thereby giving troponin levels a prognostic value[3,4].

Lobectomies through a thoracotomy incision is a very common operation in patients with lung cancer[5]. Positioning the patient and providing one-lung ventilation (OLV) pose a particular challenge[6].

The hemodynamic benefits of combining thoracic epidural anesthesia (TEA) with general anesthesia compared to general anesthesia alone are well-described, as are the benefits on intestinal perfusion and mobility, probably the reduction of sympathetic activity and response to stress, and the decreased rate of pulmonary complications[7–9].

The rationale behind this study was the analysis of the data that may lead to an increase or stabilization of troponin and other associated cardiac values during a lobectomy in ASA I and II populations.

MATERIALS AND METHODS

This prospective observational study has been approved by the Postgraduate Study Program (MSc) "Cardiopulmonary resuscitation", and the Ethics Committee of the «EVANGELISMOS" General Hospital. Data were recorded fully respecting patient anonymity. Selection of anesthesia protocol for each case was solely based on the clinical judgment of the attending anesthesiologist.

STUDY DESIGN

We selected patients who underwent lobectomy through posterolateral or anterolateral thoracotomy from November 2016 to June 2017 were included in the study.

The patients were assigned into two groups. Group 1 included patients who received general and perioperative total intravenous analgesia. Induction in these patients was performed with standard doses of propofol and rocuronium, while maintenance anesthesia was achieved using sevoflurane and repeat doses of rocuronium. Fentanyl at 3.4–3.6mcg/kg and remifentanil 20mcg/ml solution intraoperative doses were used and titrated to analgesic effect. For immediate postoperative analgesia, patients in this group received 0.12–0.14mg/kg of morphine and 1g of paracetamol and subsequently a combination of pethidine and paracetamol as needed.

Group 2 included patients who received a combination of general and thoracic epidural anesthesia. Prior to induction, an epidural catheter was placed between T4 and T7 and all patients received a 3ml 2% lidocaine test dose. Induction and maintenance of anesthesia was performed with the same doses of propofol, rocuronium and sevoflurane as in the first group and intraoperative analgesia was achieved through the same doses of fentanyl and remifentanil, but with additional epidural bolus of ropivacaine 2mg/ml solution adjusted to patient's age and BMI and an additional 50mcg of fentanyl prior to surgical incision. For the first three post-operative days we administered continuous epidural infusion of 1.95 mg/ml ropivacaine and 1.25–1.5mcg/ml fentanyl solutions at an initial dose of 4–8ml/h and titrated to analgesic effect.

Among exclusion criteria were age over 80 years, ASA class III or more, BMI extremes, sepsis or bacteraemia, prior myocardial infarction, symptomatic coronary artery disease, chronic troponin leak, COPD stage 3 or higher (FEV_1/FVC <0.70 or FEV_1 $<50\%$), baseline anemia, chronic kidney disease or acute renal injury, known chronic liver disease or any abnormal liver function tests, known coagulopathy or anticoagulation therapy, severe perioperative bleeding, perioperative hemodynamic instability requiring vasopressors and operative time more than three hours due to unforeseen surgical factors.

DATA COLLECTION

As a basic tool of this study, a data logging form was used. In this form, the patient's demographic data, namely the sex, age, weight and height of the patient, the ASA score and the COPD stage according to GINA, and the pre-operative values of troponin, CK and CK-MB, urea, creatinine, SGOT, SGPT and APTT were recorded. There was an assessment of the patient's clinical condition by an anesthesiologist and collection of laboratory results preoperatively. On the day of surgery, the anesthesia method and various perioperative events were recorded. Finally, we collected the respective laboratory values of the first and third day postoperatively.

STATISTICAL ANALYSIS

The statistical analysis of the data was performed using the SPSS for Windows statistical software (SPSS Inc., Chicago, IL).

The first part of the analysis comprises the descriptive results where the rates in each category corresponding to a qualitative variable were calculated. Mean and standard deviations for those attributes corresponding to quantitative variables were also calculated, such as age.

The second part of the analysis included the results of simple correlations (bivalent analysis). Between two variables that followed a normal distribution, t-test was performed, whereas if two continuous variables did not follow normal distribution, a Man – Whitney test was performed. When more than two variables were to be compared, ANOVA analysis was performed if normal distribution was followed and if continuous variables did not follow a normal distribution a Kruskal – Wallis test was performed. In all the controls performed, the significance level (P) was set at 0.05. Thus, all values that were less than or equal to 0.05 ($P\leq0.05$) were considered statistically significant. The regularity check was carried out using the Kolmogorov-Smirnov statistical test.

The p-value (P or p) was set ≤0.05, so all values less than or equal to 0.05 are considered statistically significant.

The values of all the measured indicators were recorded as T_0, T_1 and T_2. The time T_0 corresponds to indicator readings up to 24 hours prior to surgery, T_1 to 12-24 hours after surgery and T_2 to 48–72 hours after surgery. Practically, the time differences Δ (T_1–T_0) and Δ (T_2–T_1) are equal, i.e. T_1 has equal distances from T_0 as well as T_2 in terms of time.

RESULTS

Of a total cohort of 48 patients, 34 (70.8%) were men aged 63.5±11.6 years and 14 (29.2%) were women whose mean age was 62.9±9.2 years. Average body mass index was 26.6±3.7. In total, 17 (35.4%) patients were normal, 22 (45.8%) overweight and 9 (18.8%) obese (grade I, BMI <35).

Troponin levels were significantly lower before the onset of surgical procedure (T_0) compared to the values during and after surgery (T_2) (p=0.001). Difference between troponin levels between T_1 and T_2 was statistically insignificant (p=0.975).

Patients receiving a combination of thoracic epidural anesthesia and general anesthesia had significantly lower levels of troponin 12–24 hours (T_1) after surgery (8.9±4.1 versus 16.8±10.5, with p=0.007), while on the third post-operative day difference in troponin levels did not remain statistically significant (10.7±6.9 versus 14.8±8.3, p=0.103).

Levels of CK-MB were significantly greater (p=0.001) after surgery. Baseline hemoglobin (Hb) levels were significantly greater than at 12–24 hours postoperatively (p=0.001); standard deviations of Hb remained the smallest compared to the rest of the indices.

DISCUSSION

Based on Table 1, troponin levels were significantly lower prior to surgery relative to 12–24 hours or 48–72 hours after surgery (p=0.001). Since 2010 several studies have attempted to investigate the relationship between postoperative troponin and a possible myocardial infarction (MI). It seems that, although there is postoperative elevation of cardiac biomarkers in 5–25% of surgical patients signifying myocardial injury, most remain asymptomatic[10]. According to POISE, in which 8351 patients' cardiac biomarkers were recorded for the first three days after surgery, only 5% (415) of the patients met criteria for an MI, out of whom 65 (3%) did not experience angina or equivalent symptoms[11]. In the VISION study, only 8% of over 15,000 patients were found to have troponin leak during the first three post-operative days and only half of them met criteria for MI. These studies highlight the value of serum troponin levels as a prognostic index for post-operative cardiovascular events.

Out of 48 patients, 34 were men and 14 were women. It is noteworthy that the average age in both men and women is almost identical, with a difference of less than seven months. Although there appears to be a difference in troponin values between men and women at T_0 and especially T_1, this did not meet statistically significance (Table 2). This is an important observation, since the statistically equal ages of the two sexes can be considered a common fixed parameter. Recent researches investigate the possibility of separate examination of troponin according to sex, but there is not a proven benefit for this practise[12].

Regarding the effect of body mass index, increased baseline cardiac demand in the overweight may predispose the myocardium to tolerate stress and hypoxia. Although obesity is a risk factor for atherosclerosis and MI[13], there are studies to support the theory of myocardial preconditioning in

TABLE 2. Marker differences in relation to sex.

Variable	Male	Female	p value
cTnT, T_0	8.8 ± 4.3	6.3 ± 4.4	0.077
cTnT, T_1	12.7 ± 7.7	18.2 ± 12.9	0.074
cTnT, T_2	13.3 ± 7.9	13.8 ± 8.6	0.858
CK, T_0	103.5 ± 71.3	101.1 ± 58.4	0.912
CK, T_1	1111.6± 681.9	884.6 ± 390.7	0.250
CK, T_2	744.5 ± 586.2	583.5 ± 372.9	0.348
CK-MB, T_0	18.4 ± 7.9	15.8 ± 2.6	0.494
CK-MB, T_1	30.3 ± 19.2	26.8 ± 6.2	0.511
CK-MB, T_2	27.4 ± 28.7	22.1 ± 8.2	0.508
Hb, T_0	14.1 ± 1.5	13.1 ± 1.4	0.072
Hb, T_1	12.1 ± 1.6	11.3 ± 1.2	0.115
Hb, T_2	11.6 ± 1.7	10.9 ± 1.1	0.269

TABLE 1. Values of variables (markers) of all patients at three consecutive times T_0, T_1 and T_2.

Variable	T_0	T_1	T_2	p value
cTnT	8.1 ± 4.4	14.3 ± 9.7	13.5 ± 8.1	0.001
CK	102.8 ± 67.2	1045.4 ± 616.1	697.5 ± 534.1	0.001
CK-MB	17.5 ± 6.6	29.2 ± 16.5	25.8 ± 24.3	0.128
Hb	13.8 ± 1.5	11.8 ± 1.6	11.4 ± 1.6	0.001

obese patients[14]. In general, weight did not appear to affect cardiac enzymes in a statistically significant way. Notably, BMI extremes (BMI >35 or <20) were excluded from the study. (Table 3).

Most importantly, patients were divided in 2 study groups based on the type of anesthesia they received: 15 (31.25%) received a combination of thoracic epidural anesthesia and general anesthesia while the remaining 33 (68.75%) patients received general anesthesia alone. Patients receiving the combination of thoracic epidural anesthesia and general anesthesia had significantly lower levels of troponin 12-24 hours (T_1) after surgery, but not 48-72h (T_2) after surgery. (Table 4).

These results correlate with a metanalysis of 1173 surgical patients, according to which the incidence of post-operative MI was significantly decreased in patients who received a combination of general and epidural anesthesia[15]. Similar studies reaffirm this observation[16], although the recently published Poise-2 study[17] analyzing data from 10,010 patients, suggests that epidural blockade does not lead to better cardiovascular outcomes compared to general anesthesia.

Levels of CK-MB did not differ statistically in T_1 and T_2 ($p = 0.283$ and $p = 0.522$, respectively), while the same can be said of CK and Hb in regard to the application or not of thoracic epidural anesthesia.

The fluctuation of postoperative troponin and its association with thromboembolic events 30 days postoperatively starts to be investigated.

Until today, neither thromboembolic complications, nor myocardial injury after non-cardiac surgery (MINS) have been investigated in association with anesthesia techniques.

Botto et al studied 15,065 individuals[18] and showed that the measurement of troponin during the first three days after surgery may act as a predictor of myocardial damage as far as 30 days post-operatively. In addition to the probable cardiovascular benefits of epidural anesthesia, we may be able to both predict and mitigate cardiac injury amongst surgical patients.

TABLE 4. Marker differences in relation to the type of anesthesia.

Variable	Epidural	Not epidural	p value
cTnT, T_0	7.3 ± 3.5	8.4± 4.8	0.416
cTnT, T_1	8.9 ± 4.1	16.8 ± 10.5	0.007
cTnT, T_2	10.7 ± 6.9	14.8 ± 8.3	0.103
CK, T_0	114.7 ± 78.2	97.3 ± 62.1	0.412
CK, T_1	1103.5 ± 675.7	1018.9 ± 596.1	0.664
CK, T_2	612.2 ± 333.2	736.3 ± 604.5	0.461
CK-MB, T_0	22.3 ± 7.4	14.3 ± 3.8	0.015
CK-MB, T_1	33.1 ± 24.5	27.5 ± 11.2	0.283
CK-MB, T_2	29.1 ± 40.4	24.2 ± 10.9	0.522
Hb, T_0	13.9 ± 1.3	13.7 ± 1.6	0.668
Hb, T_1	11.8 ± 1.6	11.8 ± 1.6	0.964
Hb, T_2	11.5 ± 1.7	11.4 ± 1.6	0.845

CONCLUSION

Patients who undergo open lobectomy receiving a combination of general and thoracic epidural anesthesia appear to sustain probably less ischemic cardiovascular injury in the immediate post-operative period than patients receiving general anesthesia alone, as evidenced by significantly lower troponin

TABLE 3. Marker differences in relation to BMI.

Variable	BMI 20–25	BMI 25–30	BMI 30–35	p value
cTnT, T_0	7.5 ± 4.7	8.4 ± 4.6	8.3 ± 3.8	0.812
cTnT, T_1	16.5 ± 11.7	13.4 ± 6.9	12.3 ±1 1.5	0.503
cTnT, T_2	13.1 ± 8.8	12.5 ± 9.1	13.5 ± 8.1	0.852
CK, T_0	83.4 ± 41.3	110.4 ± 70.8	120.7 ± 92.9	0.316
CK, T_1	938.5 ± 365.2	1026 ± 682.5	1294.4 ± 803.3	0.375
CK, T_2	642.1 ± 395.8	624.7 ± 437.1	980.3 ± 865.9	0.214
CK-MB, T_0	15.5 ± 3.5	15.1 ± 4.2	27 ± 7.2	0.009
CK-MB, T_1	26.3 ± 6.4	29.5 ± 22.2	34.3 ± 12.9	0.504
CK-MB, T_2	21.8 ± 10.4	28.9 ± 34.3	25.6 ± 11.2	0.681
Hb, T_0	13.7 ± 1.5	13.5 ± 1.6	14.5 ± 1.3	0.221
Hb, T_1	11.6 ± 1.7	11.9 ± 1.2	12.2 ± 2.1	0.641
Hb, T_2	11.2 ± 1.8	11.4 ± 1.2	11.8 ± 2.1	0.622

levels at least within the first 24 hours after surgery. Significance persisted after adjustment for age, sex and BMI. This observation argues for a superiority of epidural versus non-epidural anesthesia regarding cardiovascular outcomes. On the other hand, no significant association was found between change in CK, CK-MB and Hb values and anesthetic techniques.

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