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Caspase-9 and p53 Protein Levels in Cancer Patients after Different Anesthesia Techniques

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Summary

The aim of this study was to investigate the changes in caspase-9 and p53 levels as biomarkers of pro- and anti-apoptotic pathways in the early postoperative period in patients who underwent lung surgery for malignant tumors under different types of multimodal or inhalation-intravenous anesthesia.

Material and Methods. A single-center prospective study of 22 patients aged 45–64 years was conducted at the Omsk Clinical Oncology Early Treatment and Prevention Center from January to April 2020. The participants were divided into two groups. Group 1 patients received multimodal anesthesia, which included sympathetic nerve block and prolonged epidural analgesia in the postoperative period. Group 2 patients received inhalational and intravenous anesthesia followed by systemic morphine analgesia. Serum caspase-9 and p53 protein levels were measured at four time points: before anesthesia, one, twelve, and twenty-four hours after surgery. Statistical hypotheses were tested using nonparametric (rank) analysis methods. Friedman's ANOVA was used to compare multiple time points, while the Wilcoxon test was used to compare variables between two time points in dependent samples. The Mann-Whitney test was used to assess differences between groups in independent samples. *P*-values < 0.05 were considered statistically significant. Results are expressed as median ± half interquartile range *(Me ± (LQ – UQ) / 2)*.

Results. At time point 2, caspase-9 levels were significantly higher in group 2 patients than in group 1 ($P = 0.045$). There were no significant differences between the groups at any other time points.

Conclusion. The lack of a significant difference in serum levels of caspase-9 and p53 protein at most time points between the groups demonstrates the efficacy of the anesthesia and analgesia methods used. Meanwhile, a significantly higher level of caspase-9 one hour after surgery demonstrates a greater susceptibility of patients without sympathetic blockade to activation of the apoptotic cell death program.

Keywords: inflammation; caspase-9; protein p53; multimodal anesthesia; combined inhalation and intravenous anesthesia

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

Introduction

Several critical factors affecting the human body typically cause damage by inflammation [1, 2]. Inflammationrepresents a common pathological process that is essential for the post-injury survival strategy of the body leading either to the restoration of homeostasis, i.e., recovery, or death. The latter is associated with the activation of so-called cell suicide programs. Cell death has been studied extensively over the past 25 years. In 2005, the Nomenclature Committee on Cell Death issued its first recommendations, identifying three types of cell death: necrosis, apoptosis, and autophagy. The committee's 2018 recommendations identify twelve types.

This situation can be explained by the fact that the original recommendations focused solely on the morphological changes in cells during the execution of suicidal cell programs, whereas the more recent guidelines focus on the processes that occur within the cell during death. Clearly, the identification of new types of programmed cell death could be an endless process, inextricably linked to the development of new research methods. Should modern anesthesiologists and intensivists be concerned about the complexity of cell suicide programs? Probably not. However, given the vast amount of information available on this topic, here are a few key points to remember:

- Modern oncologic surgery is highly traumatic, and similar injuries to an organism in the «wild» would always be fatal.
- Anesthesia, analgesia, and intensive care are all options for treating severe injuries.
- The primary goal of these methods is to reduce the metabolic response to injury rather than to provide «anti-stress protection».
- Metabolic responses to injury include not only hormonal changes (e. g., elevated cortisol and

catecholamine levels), but also immunological changes such as activation of cytokine cascades, expression of acute phase proteins, caspases, and pro- and anti-apoptotic proteins.

- The duration and intensity of the metabolic response to injury may affect the outcome of surgery.

Anesthesiologists should distinguish between immunogenic and non-immunogenic cell death [3]. In contrast to the elimination of dying cells by specific suicide programs (e. g., apoptosis), which does not lead to subsequent inflammatory response [4], immunogenic cell death can have negative consequences, such as widespread inflammation and overexpression of various cytokines in the early stages. While apoptosis can cause inflammation in some cases [5], the release of DAMPs (damage-associated molecular patterns) is the primary immunogenic factor that controls the balance between immunity and its absence. Furthermore, the receptors for endogenous DAMPs (heat shock proteins, histones, transcription factor A, DNA, RNA, extracellular ATP, etc.) will be the same PRRs (pattern recognition receptors) as for MAMPs [6-8]. However, various types of cell death will naturally differ in their DAMP expression profiles in response to different stimuli [6]. In any case, there will undoubtedly be a universal «signal 0» that causes local inflammation.

In the case of minor injury, activation of the cytokine cascade in the form of a balanced increase in the concentration of pro- and anti-inflammatory cytokines will trigger a local response that will lead to restoration of anatomical and functional integrity, i. e. recovery.

When an endocrine (generalized) inflammatory response develops, the bloodstream will contain large amounts of cytokines, especially if natural limiting agents (such as cortisol and adrenocorticotropic hormone) are deficient. Such a situation can act as a powerful proapoptotic signal, activating a cell suicide program.

In the best-studied form of programmed cell death, apoptosis, the induction of pro-apoptotic signals occurs via two primary pathways, extrinsic and intrinsic, and using combination of both. The apoptotic process begins with the interaction of a specific «extracellular domain and ligand» pair. An example of extrinsic pathway activation is the interaction of TNFα with specialized receptors, in particular the transmembrane receptors TNFR1 and TNFR2 [9], FAS [4], UNS5B, DCC [10] and others.

The intrinsic pathway is mediated by mitochondria-related mechanisms. A specific sequence of events leads to mitochondrial outer membrane permeabilization (MOMP), resulting in loss of functional membrane integrity, followed by release of mitochondrial proteins (DIABLO, HTRA2, cytochrome c) into the cytosol [11]. Mitochondrial membrane permeability is controlled by proteins of the Bcl-2 family, whose pro- or anti-apoptotic role is determined by the number and type of BH domains [12]. The levels of Bcl-2 family proteins are in turn regulated by the product of the tumor suppressor gene TP53, the p53 protein [1,13].

The programmed cell death (PCD) pathway is obviously executed according to one scenario. Tetramers are formed to activate initiation caspases, which in turn activate effector caspases [14]. Despite differences in the pathways leading to the pro-apoptotic signal, the process converges at a single point: the activation of initiation caspases followed by the activation of effector caspases [15]. Caspases 8, 9, 10, and 12 belong to initiators, whereas caspases 3, 6, 7, and 14 are effectors [16].

Direct p53-induced apoptosis is likely to be the first rapid phase of the inflammatory response to extensive damage. Some studies have found that in radiosensitive tissues (such as thymus or spleen), p53 translocation to mitochondria and activation of the effector caspase-3 occur very rapidly (within 30 minutes), even before sufficient p53-regulated gene products are produced. The next wave of apoptosis induction occurs 6 to 7 hours later and is associated with p53 transcriptional activity in the nucleus [17].

It appears that p53 acts at multiple levels, using different mechanisms to induce both a «rapid» inflammatory response to stressors and a «slower» but highly effective apoptotic program for damaged cells [18]. Our study considered changes in serum levels of p53 and the initiator caspase-9 as markers of potential activation of the most well-studied cell death program, apoptosis, without specifying the activation pathway, whether via specialized receptors or the mitochondrial pathway [19].

We have previously described changes in other inflammatory response markers in patients with the similar profile [20].

The next step in this research is to investigate changes in caspase-9 and p53 levels as potential indicators of inflammation in patients who have undergone lung resection for malignant neoplasms under different multimodal or balanced (inhalation and intravenous) anesthesia during the early postoperative period.

Materials and Methods

We conducted a single-center prospective study of 22 patients, aged 47–68 years, who underwent lobectomy for lung malignancies at the Omsk Regional Cancer Center from January to April 2020.

The collection of material for the study did not affect anesthesia and analgesia techniques or protocols. Patients signed the informed consent form. The local ethics committee of the Omsk State Medical University approved the use of the collected data for publication (protocol No. 4, dated 14.09.2022).

A double-blind method was used (both anesthesia and intensive care staff and laboratory staff were blinded to the group assignments).

All patients were weaned from mechanical ventilation in the operating room within 4±2 minutes after surgery. Patients were divided into two groups: the main (group 1, *N*=11) and the control (group 2, *N*=11). Random allocation of patients to the groups was performed from the general flow of patients in the ICU of the center using a random number table, ensuring the absence of selection bias.

Fig. 1 shows the study flow chart, while Table 1 details the characteristics of patients in groups 1 and 2.

Patients in group 1 received multimodal anesthesia and analgesia along with neuromuscular block and mechanical ventilation. An epidural catheter was inserted at the Th5–Th6 level to administer a three-component mixture of 0.2% ropivacaine, fentanyl, and adrenaline.

Patients in group 2 received inhalational and intravenous anesthesia based on sevoflurane and fentanyl under muscle paralysis and lung ventilation.

In the postoperative period, patients in group 1 continued to receive a three-component mixture into the epidural space for analgesia. Patients in group 2 received morphine 30 mg/day by titration.

All patients also received intravenous administration of acetaminophen, 3 grams/day. Pain intensity in all patients did not exceed 2–3 points on the VAS, and the duration of surgery and anesthesia was 90±20 minutes. Comorbidities in the groups included controlled hypertension, COPD GOLD1. The ASA class of anesthesia did not exceed III (see Table 1).

Patients with comorbidities such as diabetes mellitus, postobstructive pneumonia, ischemic heart disease with II and greater class, and those taking beta-blockers or with intraoperative blood loss greater than 500 mL were excluded from the study.

Four study time points were identified: before induction of anesthesia, and at 1, 12, and 24 hours postoperatively. At these time points, serum levels of caspase-9 and p53 protein were measured.

Serum concentrations of caspase-9 and p53 protein were analyzed by the sandwich enzyme-linked immunosorbent assay (ELISA) method using test kits on the Multiscan Fc Immunological Analyzer (Thermo Fisher Scientific Corporation, USA). The caspase-9 ELISA kit used was from Cloud-Clone Corp., USA (Lot L 190226123), and the p53 (TP53) ELISA kit was also from Cloud-Clone Corp., USA (Lot L 190226138).

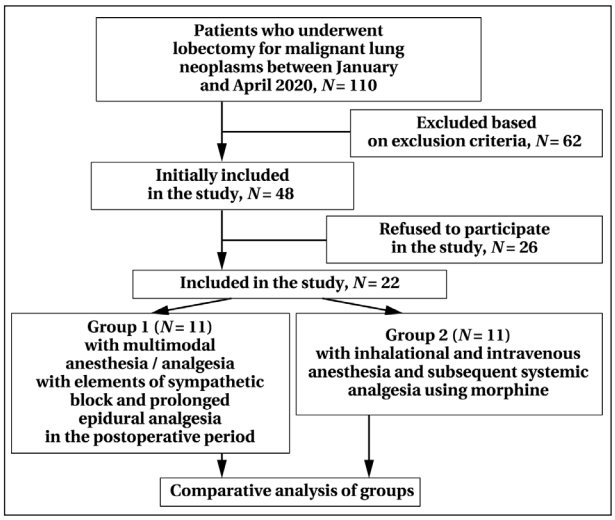

Fig. Study flowchart.

The study did not use standard checklists such as CONSORT or STROBE, as decided by the research team, which is permissible for studies with small sample sizes. The study was limited by the lack of an a priori sample size calculation and did not have a registered protocol.

Statistical analysis included tests of distribution of variables (Kolmogorov–Smirnov and Shapiro–Wilk tests) in the study groups, as well as variance values. Given the small sample size (*N*=11), non-normal distributions and unequal variances, robust non-parametric (rank-based) statistical methods were used. Statistical hypothesis testing was performed using the Wilcoxon signed-rank test (two-sample nonparametric test) for paired comparisons between two points, and Friedman's ANOVA for comparisons between four points. Differences between independent groups 1 and 2 at identical time points were assessed using the Mann–Whitney *U* test. The null hypothesis was rejected for paired comparisons between the two groups when $P < 0.05$

Table 1. Patient characteristics.

Parameter	Values in groups		*P*-value
	Group 1, *N* = 11	Group 2, *N* = 11	
Male sex, *N* (%)	8 (72.7)	9 (81.8)	0.62
Female sex, *N* (%)	3 (27.3)	2 (18.2)	
Age, years (min–max)	52–68	47–68	0.29
Comorbidities, *N* (%) (controlled hypertension, COPD GOLD1)	6 (54.5)	7 (63.6)	0.67
ASA score, points	3	3	1.0
Pain intensity on VAS, points	2–3	2–3	1.0
Duration of surgery, min	90±20	90±20	1.0

Note. Data are expressed as *Me* ± *(LQ – UQ)* / 2. No significant differences were found between groups; $P > 0.05$ (χ^2, Fisher, Mann–Whitney tests).

(using a two-tailed P value), and for multiple comparisons of study points with correction for the number of paired comparisons when $P < 0.013$ (using the Bonferroni correction). Data are presented as *Me* ± *(LQ — UQ)* / 2, i. e. the median ± half of the interquartile range. Statistical analyses were performed with STATISTICA, StatSoft, Inc. (2007), version 8.0.

Results

Results are shown in Table 2.

The analysis of the data obtained showed the following results. At the first time point (before induction of anesthesia), there was a high degree of similarity in the changes of the studied variables, indicating that the patients in both groups were comparable. The inclusion criteria used for the groups showed that none of the patients had values for the studied parameters that exceeded the upper reference limits. It is important to note that the study was performed before the first case of COVID-19 was registered in the region.

At the second time point (one hour postoperatively), significant differences between the groups were observed. Patients in the second group, who received inhalational and intravenous anesthesia with sevoflurane and systemic morphine-based analgesia, showed a significant difference in one of the parameters (caspase-9) compared to patients in the first group. However, p53 protein levels in all patients at this time point were comparable to normal and did not exceed the reference limit of 0.78 pg/mL.

At the third time point (12 hours postoperatively), patients in both groups showed statistically significant similarity in the two variables studied. None of the values in the 22 cases exceeded the reference limits.

At the fourth time point (24 hours postoperatively), no significant differences were observed between the first and second groups. All measured parameters remained within their respective reference ranges.

Discussion

The lack of difference in p53 protein levels between the groups of operated patients can be interpreted in two ways. First, it could mean that both types of anesthesia/analgesia provided adequate protection to the organism. Alternatively, it could indicate the absence of DNA damage capable of causing cell cycle arrest at any of the time points tested. As a result, there was no «need» for p53 overexpression to maintain genome stability.

Another possible explanation is discussed below. It is well known that p53 is a short-lived protein [21], with elevated levels lasting only 5 to 20 minutes, depending on the cell type. A larger number of sampling time points could have captured transient periods of p53 overexpression, potentially revealing significant differences between groups. However, the time points used in this study were previously defined and justified in our previous research [20–23].

The short lifespan of p53 has been attributed to a negative autocrine feedback loop involving the MDM2 protein, a key ubiquitin ligase responsible for p53 degradation [21]. This feedback mechanism is activated in response to stress, ensuring that the organism's «protective strategy» remains within physiological limits. However, during stress, protein kinases phosphorylate serine residues, disrupting the interaction between p53 and MDM2 [24]. This disruption causes p53 to accumulate intracellularly, allowing the coordination of multiple signaling pathways in response to cellular damage [21, 25]. Unfortunately, the ELISA method used in this study measures serum p53 levels but does not provide information on its functional activity [26].

In mammals, both major apoptotic pathways — extrinsic (receptor-induced) and intrinsic (mitochondrial) — use a caspase cascade [27]. The key feature of this cascade is its stepwise activation: pro-caspases are cleaved to active inducer caspases (such as caspase-9), which then activate effector caspases. Effector caspases are responsible for the

Table 2. Changes in serum concentrations of caspase-9 and p-53 in patients of groups 1 and 2, *Me (LQ – UQ)* / 2.

Study time point	Values in groups		*P*-value
	Group 1, *N* = 11	Group 2, *N* = 11	
Caspase-9 (reference range: 0–0.312 pg/mL)			
1	0.22 (0.13–0.25)	0.13 (0.10–0.23)	0.14
2	0.21 (0.17–0.25)	0.14 (0.11–0.22)	0.045*
3	0.14 (0.11–0.18)	0.15 (0.14–0.17)	0.38
4	0.16 (0.11–0.19)	0.14 (0.10–0.17)	0.22
ANOVA	χ^2 (d_f = 3) = 6.82; P = 0.077	χ^2 (d_f = 3) = 2.28; P = 0.52	—
p53 (reference range: 0–78 pg/mL)			
1	52.60 (45.40–61.70)	51.30 (43.50–70.60)	0.82
2	58.40 (50.20–68.10)	47.80 (45.00–69.70)	0.41
3	47.80 (44.50–61.70)	55.90 (34.00–66.30)	0.72
4	50.00 (43.10–65.00)	56.10 (45.80–77.60)	0.72
ANOVA	χ^2 (d_f = 3) = 6.69; P = 0.083	χ^2 (d_f = 3) = 1.15; P = 0.77	—

Note. * — statistically significant difference between groups (Mann–Whitney test) at $P < 0.05$. ANOVA — one-way Friedman analysis of variance for dependent samples (used for dynamic observation across time points).

physical disassembly of cell structures. Caspase-9, as a direct activator of effector caspases, is critical in translating the death signal into the first proteolytic event, making its regulation diagnostically relevant [27].

Furthermore, there is evidence that caspase-9 influences both programmed cell death and survival strategies such as autophagy [28, 29].

Practical limitations prevent the real-time study of various components of host defense mechanisms in response to tissue injury. Most of these methods involve sequential processes that take a certain amount of time. However, the identification of patterns in the early postoperative period using different anesthesia/analgesia methods, based on previous results, has the potential to improve surgical outcomes. One study found that the analgesic methods used were both effective and safe from a pathophysiologic standpoint for patients undergoing lung resection surgery [20]. Our previous research has shown that epidural analgesia provides strong antinociceptive protection, but may also induce an endocrine response that manifests as a widespread inflammation [22, 23].

Conclusion

Elevated levels of the initiator of caspase-9 one hour after lung resection surgery suggest an increased inflammatory response to tissue injury in patients without sympathetic blockade. The lack of significant differences in serum caspase-9 and p53 levels 12 and 24 hours after surgery demonstrates both the effectiveness of the anesthesia and analgesia methods used and the localized nature of the inflammatory response, which remained paracrine and limited to the site of tissue injury.

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