

**International Conference on Health & Medical Research 2020**



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## Management of Skin Cancer by Agonists PF 5-HT<sub>1A</sub> and Antagonists of 5-HT<sub>2A</sub> Receptors

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### Abstract

Serotonin (5-hydroxytryptamine, 5-HT) is an essential neuromodulator that can act as a growth factor for skin cancer, since its skin receptors may be involved in UV-induced immunosuppression, DNA damage, oxidative stress and cells proliferation. 1-(1-Naphthyl)piperazine (1-NPZ) is both an agonist of 5-HT<sub>1A</sub> and antagonist of 5-HT<sub>2A</sub> receptors that has shown promising effects by inhibiting UV-induced immunosuppression and, consequently, photocarcinogenesis. Melanoma arises from epidermal melanocytes, which are the main producers of serotonin in the skin and possess both 5-HT<sub>1/2A</sub> receptors. Ultradeformable vesicles are novel advantageous nanosystems capable of improving the dermal and transdermal delivery of several drugs. Transethosomes descend from both transfersomes and ethosomes, thereby having pioneering permeation-enhancing properties due to the presence of an edge activator and an alcohol. Dmsosomes are another new type of lipid vesicles containing dimethyl sulfoxide DMSO which acts directly on the skin as a penetration enhancer. The aim of this study was to investigate the therapeutic effect of 1-NPZ on human MNT-1 melanoma cells, and posteriorly develop 1-NPZ-loaded transethosomes (NPZ-TE) and dmsosomes (NPZ-DM) as novel topical delivery nanocarriers for the treatment of melanoma. The exposure conditions of 1-NPZ as well as cell viability were evaluated by MTT assay. Cell-cycle dynamics, reactive oxygen species production and apoptosis were all evaluated by flow cytometry. RT-PCR was also performed to quantify the expression levels of genes involved in immunosuppressive events and cancer progression. Treatment with 1-NPZ for 24 h reduced cell viability and induced apoptosis on MNT-1 cells, in a dose-dependent manner. 1-NPZ mediated S-phase delay in cell-cycle dynamics and increased ROS production. Moreover, the expression of COX-2 increased significantly following treatment with 1-NPZ. NPZ-TE and NPZ-DM were characterized based on the evaluation of the mean vesicles size and zeta potential by DLS. Vesicle deformability was assessed by pressure driven transport, whereas rheology studies were performed by viscometry. Spectrophotometry and HPLC were both used to determine lipid and drug entrapment yields, respectively. *In vitro* topical delivery studies were achieved using Franz diffusion cells and pig skin. Either NPZ-TE or NPZ-DM showed positive results in terms of mean size, zeta potential, deformability and rheology. 1-NPZ entrapment yield was 90.6% for NPZ-TE and 95.8% for NPZ-DM. *In vitro* data also exhibited an improved penetration of 1-NPZ into newborn pig skin, especially by NPZ-TE. In summary, this study revealed the potential of 5-HT<sub>1/2A</sub> receptors as therapeutic targets for the treatment of melanoma, identifying 1-NPZ as a promising chemotherapeutic agent.

### Keywords:

Skin cancer;  
5-HT<sub>1/2A</sub> Receptors;  
1-NPZ;  
Apoptosis;  
Topical Delivery.

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## Initial Results from Comparison of Antioxidant Markers in Saliva and Plasma in Patients with Periodontal Diseases

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### Abstract

Chronic periodontal diseases are very common and, if untreated, can lead to premature tooth loss. This in turn leads to selective food intake, nutritional deficiency and associated health complications. Relatively few studies have been devoted to this issue, but those that do converge on identifying oxidative stress in patients. This is common in all oral inflammatory diseases and may then lead to systemic changes. The aim of this study was to compare changes in selected antioxidant markers (superoxide dismutase, glutathione peroxidase, glutathione reductase, reduced glutathione) in saliva and plasma from patients with diagnosed gingivitis, a chronic and aggressive form of periodontitis. Initial results of the study come from analyses in a small number of patients, which is likely also the reason for the lack of statistical significance in the differences between parameters obtained in experimental groups and the control group. Even so, it is apparent that oxidative stress is indicative of changes in the activities of antioxidant enzymes relative to reduced glutathione concentrations. Moreover, there are positive correlations between saliva and plasma superoxide dismutase, glutathione peroxidase and glutathione reductase activities. This would allow for the dissemination of results within research groups in favour of analyses of more readily available biological material from patients.

### Keywords:

Antioxidant Enzyme;  
Antioxidant Marker;  
Parodontitis;  
Periodontal Disease;  
Reactive Oxygen Species;  
Saliva.

## 1. Introduction

Chronic periodontitis is one of the most common periodontal diseases worldwide, leading to the loss of supportive tissues of the teeth and the teeth themselves [2, 5]. The main cause of this disease is the presence of microbial plaques which contain bacteria which cause inflammatory changes in the gums and consequent bone damage [19, 29]. Symptoms of chronic periodontal disease are gingivitis, alveolar bone resorption and the presence of periodontal pockets. In addition, there are other unconventional symptoms such as dental mobility and pain. Its severity and prevalence vary considerably between populations [2], which may, in fact, be due to differences in data collection methods and patient selection criteria.

The bacteria considered to be initiating factors of periodontitis include the gram-negative anaerobic bacteria *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans*. Inflammatory reactions were also observed after stimulation by *Bacteroides forsythus*, *Prevotella intermedia*, *Peptostreptococcus micros* and *Fusobacterium nucleatum* [16]. Hiranmayi et al. [11] also found the involvement of other pathogens in the development and progression of periodontitis such as *Cryptobacterium curtum*, *Dialister pneumosintes*, *Filifactor alocis*, *Mitsuokella dentalis*, *Slackia exigua*, *Selenomonas sputigena*, *Solobacterium moorei*, *Treponema lecithinolyticum*, and *Synergistes*.

The incidence of periodontitis is also related to other factors, e.g. high blood pressure, high cholesterol, diabetes, genetic factors and obesity [23]. Periodontitis is considered a classic complication of diabetes [18] due to its action as

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a metabolic stressor that increases insulin resistance or as a continuous source of secretion of inflammatory markers. These may then enhance the cytokine response mediated by the end products of advanced glycation [21]. Chronic periodontitis is also an independent risk factor for cardiovascular disease involved in the development of systemic inflammatory mediators. Moreover, some of the same bacteria were found in periodontal pockets and atherogenic plaques [10, 12, 24]. While diet, physical inactivity and smoking are also considered to be risk factors [28], individuals exposed to a higher level of stress tend to neglect oral hygiene, change their eating habits, and smoke; all of which affect the entire immune system negatively [26]. Despite this, age and gender are among the most prominent factors. The production of reactive oxygen species (ROS) and the incidence of chronic inflammatory diseases increase with age. In men, the cause of periodontal disease has been shown to be poor oral hygiene in many cases [22, 30].

Periodontitis is a chronic inflammatory process associated with the production of ROS. Factors with a demonstrable link to it are also involved in the production of ROS. The aim of this study was to determine the effectiveness of selected antioxidant markers against ROS in saliva from patients with periodontitis and to compare them with values in healthy individuals.

## **2. Materials and Methods**

The study was approved by the Ethics Committee of Louis Pasteur University Hospital in Košice under no. 2018/EK/2010. Potential study participants were familiarised with the aim of the research prior to enrolment, and sampling took place after informed consent was signed. Blood samples were taken from the antecubital vein in order to determine standard and biochemical parameters and selected antioxidant markers. The collection of saliva (50 patients) and blood (44 patients) took place in the periodontology department of the 1st Dental Clinic of the University hospital in the morning between 7:00 – 9:00. Prior to collection, patients fasted without drinking fluids or brushing their teeth. During the collection, the patients were seated upright with their head slightly bent and spitting free-forming saliva in the mouth for 10 minutes. Saliva was then transported to the biochemical laboratory on ice. Patients were grouped according to clinical signs.

The first group consisted of healthy individuals (13 saliva and 12 plasma samples). Patients with gingivitis were the second group (12 saliva and 9 plasma samples). In the clinical picture, gingival bleeding and possible calculus deposits were observed. In the CPITN index examination, values of 1: (indicative of any bleeding), and 2: (indicative of calculus deposits), were reported in most sextants. The third group (CP) consisted of patients with chronic periodontitis and were found to have periodontal pockets during the clinical examination (16 saliva and 15 plasma samples). Values of 3: (pocket depth up to 6 mm), and 4: (more than 6 mm), were measured according to the CPITN (Community Periodontal Index of Treatment Needs). Alveolar bone resorption with concomitant gingivitis was observed via X-ray. The fourth group (AP) consisted of patients with aggressive periodontitis (9 saliva and 8 plasma samples). We observed deep periodontal pockets (pocket depth over 6 mm) predominantly in relatively young individuals. The gingiva was pale pink with possible point-like bleeding upon stimulus and the widespread damage to the periodontal tissues did not respond to oral hygiene. Groups with periodontitis, either chronic or aggressive, represented a generalised form.

Protein concentration in saliva and plasma was determined by a bicinchoninic assay. The activities of glutathione peroxidase (GPx, EC 1.19.1.9), glutathione reductase (GR, EC 1.8.1.7) were determined according to the kit manufacturer procedures (Sigma-Aldrich, Germany), and superoxide dismutase (SOD, EC 1.15.1.1) by the SOD Assay Kit- WST (Fluka, Japan). The reduced glutathione (GSH) concentration was determined by the method of Floreani et al. [7]. After testing the normal distribution of values in groups, the Kruskal-Wallis test was used to determine the differences in the groups within each parameter and the Mann-Whitney U test to compare the individual parameters between groups. Results were considered significant at  $p < 0.05$ . The Spearman correlation test was used to determine the possible relationship between saliva and plasma measured parameters.

## **3. Results and Discussion**

Patient samples obtained so far are relatively low, but taking blood samples from patients at the dentist has been problematic. If patients did not wish to provide blood, we proceeded to evaluate and compare parameters at this stage, as further such comparison is unlikely to be possible. Tables 1 and 2 provide descriptive characteristics of the four measured parameters in the four saliva and plasma patient groups. No significant differences were found in individual parameters between groups, or between the given parameters in saliva and plasma. However, according to median values there is a trend of increased SOD activities in patients with chronic periodontitis in both saliva and plasma (Table 1). A similar trend can be seen in GSH concentrations (Table 2). While GPx and GR activities do not show same increasing shift in activities for both chronic and aggressive periodontitis.

Positive correlation has been demonstrated between the progression of periodontitis and serum SOD activity in experimental animals [31]. This has been confirmed in human serum, gingival sulcular fluid and saliva [1, 6, 8, 14, 32]. As observed in an animal model under experimental conditions, induction of SOD resulted in the inhibition of

periodontitis [27]. Thus, SOD is considered a potential diagnostic marker of periodontitis.

**Table 1. Activities of superoxide dismutase and glutathione peroxidase in saliva and plasma of patients with periodontal disease. AP – aggressive periodontitis, CP – chronic periodontitis, GPx – glutathione peroxidase, med (min – max) – median (minimum – maximum), P – statistical significance, SOD – superoxide dismutase.**

Group/ parameter	SOD ( $\mu$ kat/ mg prot) med (min – max)		P saliva vs. plasma	GPx ( $\mu$ kat/ mg prot) med (min – max)		P saliva vs. plasma
	saliva	plasma		saliva	plasma	
Control	0.0580 (0.004 – 0.151)	0.1870 (0.1300 – 0.2700)	1.7068	0.8740 (0.2743 – 7.4479)	0.2485 (0.0146 – 4.1228)	0.2460
Gingivitis	0.0640 (0.0170 – 0.1040)	0.2420 (0.0680 – 0.3200)	0.3371	1.2743 (0.2469 – 2.2531)	0.2778 (0.1754 – 0.9064)	0.3271
CP	0.1440 (0.0210 – 0.3390)	0.1600 (0.1170 – 0.2910)	0.7718	0.5190 (0.0439 – 1.7105)	1.0965 (0.1170 – 3.9474)	0.4593
AP	0.1570 (0.1090 – 0.1980)	0.1490 (0.1300 – 0.1560)	0.7949	1.7105 (0.0439 – 3.6988)	0.9503 (0.1023 – 2.1199)	0.7263
P	0.4796	0.8556		0.6902	0.7805	

We determined the selenium isoforms of glutathione peroxidase according to the kit composition. Glutathione peroxidase is an enzyme that catalyses the reduction of hydrogen peroxide using glutathione as a reducing agent [25]. Almerich-Silla et al. [3] found the highest values of glutathione peroxidase in the group of patients with chronic periodontitis compared to the healthy group and patients with gingivitis. The initial results of our study point to a difference from these studies, although the number of patients examined so far is low. Nevertheless, the nature of the enzymes' action suggests glutathione peroxidase inhibition due to excess substrate (peroxides). Glutathione reductase activity is then affected as a compensatory mechanism for the production of reduced glutathione as a direct reducing agent.

A second explanation can be found in the assay methodology used to determine the activity of the selenium isoforms of glutathione peroxidase and not the total, so the overall activity of glutathione peroxidases could be increased. However, a positive correlation was found between SOD activities in plasma and saliva ( $r = 0.677$ ), and GPx ( $r = 0.5234$ ) and GR ( $r = 0.6417$ ).

**Table 2. Activities of glutathione reductase and concentrations of reduced glutathione in saliva and plasma of patients with periodontal disease. AP – aggressive periodontitis, CP – chronic periodontitis, GR – glutathione reductase, GSH – reduced glutathione, med (min – max) – median (minimum – maximum), P – statistical significance.**

Group/ parameter	GR ( $\mu$ kat/ mg prot) med (min – max)		P saliva vs. plasma	GSH (nmol SH/ mg prot) med (min – max)		P saliva vs. plasma
	saliva	plasma		saliva	plasma	
Control	0.7407 (0.1608 – 2.1138)	1.1015 (0.3129 – 1.9583)	0.5961	0.1652 (0.0835 – 0.7498)	0.3536 (0.2206 – 1.2629)	0.2263
Gingivitis	0.6902 (0.4321 – 10.3175)	1.2391 (0.1681 – 4.1209)	0.6455	0.1260 (0.0414 – 0.9926)	0.3863 (0.1671 – 1.1029)	0.5755
CP	0.8602 (0.7373 – 1.1311)	0.9619 (0.5459 – 1.6588)	0.8415	0.2834 (0.0189 – 0.5980)	0.4322 (0.2057 – 1.4117)	0.6101
AP	1.2118 (0.1449 – 4.3016)	0.8184 (0.2083 – 1.4035)	0.5552	0.5181 (0.2280 – 1.8919)	0.2783 (0.1992 – 1.8615)	0.7795
P	0.9667	0.9337		0.7975	0.9126	

Also, the biochemical parameters determined in routine examinations (Table 3) do not show statistically significant differences between groups, especially given the small numbers of patients examined. Nevertheless, some of the value distribution can be pointed out. First, the median of albumin values is higher in patients with chronic and acute periodontitis. Studies by Kaur et al. [15] and Kolte et al. [17] showed that there is association between chronic periodontitis and serum albumin concentrations in terms of inflammatory conditions in an organism, and with

nutritional deficiency resulting also from the number of teeth and condition of the oral cavity. Second, median values of alkaline phosphatase (ALP) are shifted higher in patients with chronic and aggressive periodontitis. Recently, Malhotra et al. [20] confirmed that ALP positively correlates with probing depth and is a suitable marker for identifying inflammatory sites in the oral cavity. Compared to healthy individuals, ALP levels are higher not only in saliva but also in the serum of patients with chronic periodontitis [13]. Third, it is evident that the medians of the C-reactive protein values in patients with periodontal disease (also the maximum value in chronic periodontitis) are higher than in healthy individuals. This would be consistent with a recent study by Bolla et al. [4], confirming higher serum CRP values in patients with chronic and aggressive periodontitis as compared to healthy subjects. Also noteworthy is the shift of the median to higher values for total cholesterol, more significantly in patients with chronic periodontitis, which would correspond to the confirmed association between hyperlipidemia and periodontal disease [9].

**Table 3. Serum concentrations of some biochemical parameters. AP – aggressive periodontitis, ALP – alkaline phosphatase, CP – chronic periodontitis, med (min – max) – median (minimum – maximum), P – statistical significance.**

	Control med (min - max)	Gingivitis med (min - max)	CP med (min - max)	AP med (min - max)	P
Creatinine (μmol/l)	62.8 (53 – 85.6)	66 (53 – 85.6)	68.95 (46.9 – 85.6)	58 (49.8 – 81.9)	0.9832
Albumin (g/l)	46.1 (43 – 49.9)	47 (43.3 – 47.6)	42.3 (38.7 – 43.6)	42.75 (42.5 – 45.6)	0.4247
ALP (μkat/l)	1.07 (0.45 – 1.75)	1.02 (0.81 – 1.52)	1.35 (0.88 – 1.6)	1.54 (0.82 – 1.91)	0.9205
Cholesterol (mmol/l)	4.25 (3.42 – 6.56)	4.1 (3.67 – 6.14)	5.86 (3.79 – 8.89)	4.71 (3.86 – 6.81)	0.6771
CRP (mg/l)	0.57 (0.22 – 9.71)	1.15 (0.3 – 5.69)	1.81 (0.71 – 16.31)	1.28 (0.93 – 5.31)	0.9486
Na (mmol/l)	138.3 (136.2 – 140.9)	137.9 (135.8 – 140)	139.1 (135.7 – 142.5)	137.6 (136.3 – 144)	0.9844
K (mmol/l)	4.4 (4 – 4.7)	4.2 (3.8 – 4.8)	4.3 (3.9 – 4.6)	4.4 (4.2 – 4.8)	0.8677
Cl (mmol/l)	103.8 (99.4 – 107.1)	103.4 (99.7 – 107)	104.5 (101.8 – 108.1)	102.3 (99.4 – 107.3)	0.9662
Ca (mmol/l)	2.47 (2.41 – 2.56)	2.48 (2.42 – 2.55)	2.38 (2.3 – 2.49)	2.52 (2.37 – 2.58)	0.8619
Mg (mmol/l)	0.84 (0.77 – 0.95)	0.84 (0.78 – 0.88)	0.82 (0.75 – 0.91)	0.85 (0.07 – 0.88)	0.9927
P (mmol/l)	1.11 (0.76 – 78.5)	1.05 (0.97 – 1.21)	1.08 (0.94 – 1.21)	0.86 (0.65 – 1.24)	0.9975

## 4. Conclusion

The nature of the effect of antioxidant enzymes points to the conditions of oxidative stress in patients with periodontal diseases, which is compensated by the reduced glutathione concentration. However, the sample size needs to be expanded. Maintaining a balance between increased production of reactive oxygen species and an adequate response to antioxidant mechanisms is important through the course of the disease, both against bacterial infection and in preventing tissue destruction. Recent results indicate a positive correlation between SOD, GPx and GR activities in saliva and plasma, which could facilitate the collection and analysis of biological material in favour of something more readily accessible to patients.

## 5. Acknowledgements

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## Monitoring of Post-operative Residual Neuromuscular Blockade after Application of Intermediate Non-depolarising Myorelaxants

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### Abstract

The complications of persistent residual neuromuscular blockade, such as pneumonia, develop a few days after surgery and are rarely linked to it. The only method of prevention, therefore, is monitoring muscle relaxation. Age, physical status, duration of operation, and low body temperature are among the risk factors for post-operative residual curarisation (PORC). The train-of-four ratio, used in monitoring muscle activity under nerve stimulation, is considered standard in the assessment of the effect of neuromuscular blocking agents on neuromuscular transmission. As studies providing basic data on the extent to which PORC is present in our workplace are still missing, our study was focused on monitoring the occurrence of PORC in our post-anaesthesia care unit with respect to some risk factors. In a sample of 150 patients, more frequent occurrence of PORC was found in women after surgical procedures lasting up to 120 minutes. Patient age and physical status also had a significant effect on the prevalence of ( $p = 0.0157$ ). With respect to the relaxants, PORC was found more frequently following administration of atracurium, while pharmacological decurarisation was more often achieved with neostigmine. An interesting finding was the more frequent occurrence of PORC for doctors performing anaesthesia without a certified examination, albeit without statistical significance. Residual neuromuscular block is a persistent problem. The severity of its occurrence is also underlined by the risk factors present, which this study has shown primarily to be the patient's physical status. Therefore, monitoring muscle relaxation is desirable.

### Keywords:

Post-operative Residual Curarisation;  
Muscle Relaxants;  
Neuromuscular Blockade;  
Train-of-four Ratio.

## 1. Introduction

Post-Operative Residual Curarisation (PORC) is characterized as the persistence of neuromuscular block with prolonged postoperative effect following administration of muscle relaxants. As reported by Plaud et al. [26] blockade may persist in up to 50% of cases, depending on the type of NMBA, reversal agent, and neuromuscular monitoring. This is also evident when using intermediate-acting NMBA [11, 21], and can lead to increased morbidity and mortality in patients [29].

There are several reasons to monitor the depth of muscle blockade. Iatrogenic respiratory failure occurs after Neuro Muscular Blocking Agent (NMBA) administration. Sometimes, despite the experience and knowledge of an anaesthesiologist, the effect of muscle relaxants is difficult to predict because of the great difference in sensitivity of individual patients. Even after sufficiently long time following administration of a single dose, there is no guarantee of the cessation of muscle blockade and full recovery of muscle strength. Clinical examination is often insufficient to objectively determine the time at which NMBAs were metabolized and their effect no longer present [1]. The Train-of-four (TOF) pattern of the stimulation response to the ulnar nerve is commonly used to determine PORC [29].

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Considering the findings that recovery of the larynx and upper oesophagus muscles is not complete, even when the patient maintains ventilation within normal limits, PORC was determined as a TOF ratio (T4/T1) of less than 0.9 [13, 22, 28]. When using the technique of measuring acceleration, or acceleromyography, the indication of adequate neuromuscular recovery is up to 1.0 or more [9].

Non-depolarizing neuromuscular blockers (NDBAs) are commonly used to facilitate endotracheal intubation and during procedures under general anaesthesia to ensure adequate surgical conditions or to optimize ventilation support [4]. By application of non-polarizing muscle relaxants (NDR), nicotinic acetylcholine receptors are occupied by competitive blockade. According to the chemical structure, they are aminosteroids or tetrahydroisoquinoline derivatives. Intermediate-acting NDBAs, such as atracurium, are eliminated via ester hydrolysis or Hoffman elimination; vecuronium and rocuronium are eliminated by the biliary system; and less than 10% of atracurium is excreted unchanged via the renal and hepatic routes [7, 15]. Several factors influence their effect as well as the reversal of neuromuscular block: these include the type of muscle relaxant used, re-administration, and individual patient variability. Of particular interest are drug interactions, co-morbidity, and condition of the patient undergoing anaesthesia. Prolongation and delay of degradation have been shown to be associated with the administration of magnesium, calcium-channel blockers, hypothermia, combination with inhalation anaesthetics, antibiotic therapy, age, obesity, acid-base balance disorders, electrolyte imbalance, dehydration, and neuromuscular disease [27].

The occurrence of PORC is clearly established in the literature. The aim of this work is primarily therefore to determine the incidence of postoperative curarisation in the post-anaesthesia care unit (PACU) at our department.

## **2. Materials and Methods**

A prospective, non-randomized and observational study was carried on of patients from the operating rooms of Louis Pasteur University Hospital (UNLP) in Košice. The study was approved by the Ethics Committee of UNLP, Košice, under the number 115/EK/18.

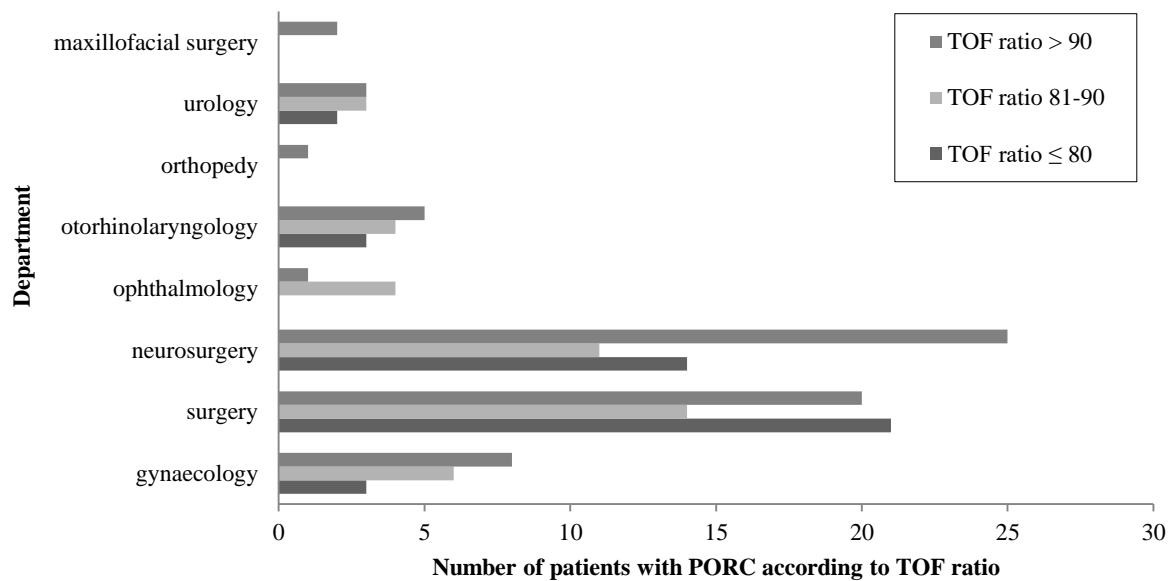
All participants underwent surgery under general anaesthesia using NDBAs (rocuronium and atracurium). All participants were extubated in the operating room and transported to the PACU accompanied by an anaesthesiologist. Here, patients were immediately connected to a vital-signs monitor. They were given oxygen by face mask as part of oxygen therapy and a TOF-Watch muscle relaxation monitor was attached to the forearm according to current recommendations. The ulnar nerve was stimulated (4 pulses of 0.2  $\mu$ s duration, 2 Hz, 50 mA) by acceleromyograph TOF-Watch® (Organon, Swords Co., Dublin, Ireland). Three consecutive TOF measurements were taken 15 seconds apart. Subsequently, these measurements were averaged.

Information was recorded about the operating room, gender, age, American Society of Anaesthesiologist Physical Status Classification (ASA), BMI calculated from information gained from the pre-anaesthesia examination (weight and height), length of surgery, and body temperature. Information was gathered about the type of relaxant used, whether it was used only once at the time of anaesthesia administration or repeatedly during the procedure, decurarisation of the patient (whether given only the so-called "small decurarisation" or "large decurarisation"), and use of sugammadex. At low TOF ratios, patients' clinical conditions were monitored for longer period and patients were released from the recovery room after reaching TOF ratios  $\geq 0.9$ . We used Mann-Whitney and Kruskal-Wallis non parametric tests to compare outcomes from the distribution of patients into groups based on relevant parameters.

## **3. Results and Discussion**

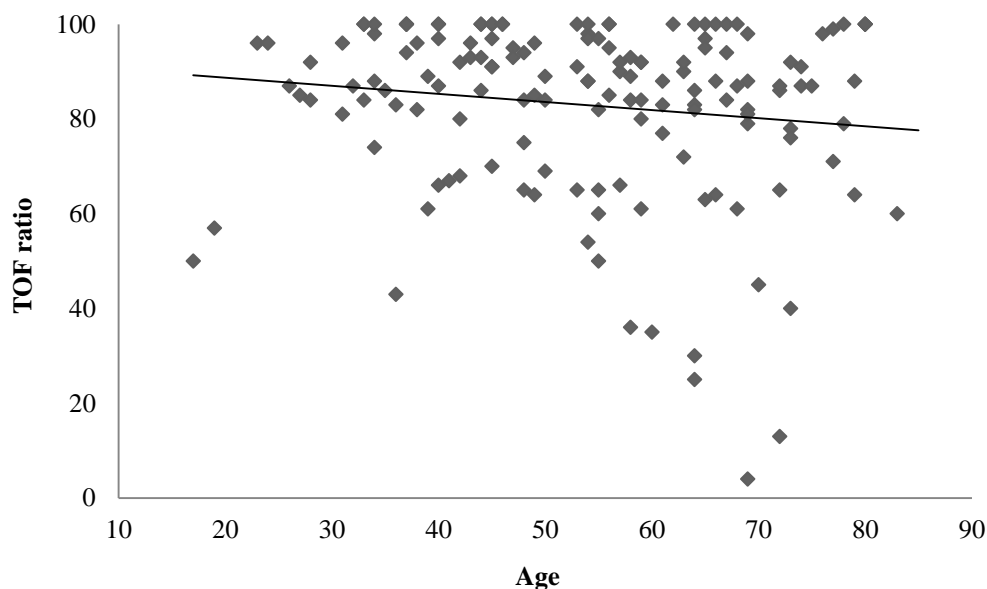
A total of 150 patients were enrolled, of which 79 were women and 71 men. The incidence of PORC was 60.8% in women and 50.7% in men. Figure 1 shows the representation of patients from individual operating rooms. 37% of patients underwent surgery in the surgical operating room, 34% in neurosurgical intervention, 16% in urological-gynaecological surgery, and the remaining 23% operation in other hospital departments. The comparison also shows the highest proportion of patients with TOF ratio  $< 0.9$  who underwent neurosurgical or other surgical intervention.

Several factors contribute to the incidence of PORC depending on the type of surgery. Ensuring optimal muscle relaxation for various surgical procedures is challenging due to the variability of patient responses to NMBA [3, 5]. Compared to the adductor pollicis musculus, the dose required to relax the diaphragm, the duration of action, and recovery of activity are different [8, 17].



**Figure 1. Occurrence of PORC in individual hospital operating rooms.**

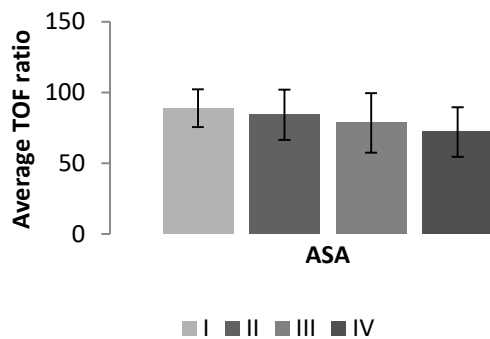
Patient age was another of the parameters monitored and a direct relationship between PORC and age has already been reported. Time required for full recovery in patients aged over 65 years is longer after administration of rocuronium and vecuronium [2, 10]. Recently, Murphy et al. [24] confirmed that, although PORC occurred at an increased rate in young and elderly patients, the incidence of PORC and other complications have been associated with elderly patients. This trend has also been demonstrated in our patient group where patients were divided into 6 groups (up to 30 years, -40, -50, -60, -70 and over 70 years) (linear trend line in Figure 2). However, our study found no statistically significant differences in the incidence of PORC due to age distribution ( $p = 0.9421$ ). This is related to lowered metabolism and thus longer elimination of NDBA.



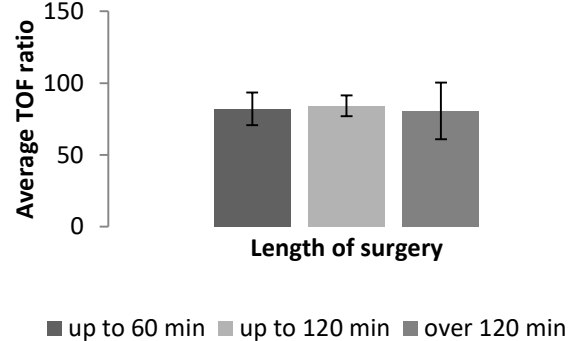
**Figure 2. Correlation between TOF ratio values and patient age (years).**

As can be seen in Figure 2, three patients deviated from the norm. Two had primarily measured low TOF ratios, but with good muscle strength. These patients were followed up more closely and had a TOF ratio of 85-87 measured after 5 minutes without pharmacological intervention. However, the youngest patient in the sample, at 17 years old, also had clinical manifestations of PORC and was pharmacologically decuricised; nevertheless, low TOF values persisted over some time. In this case, we could assume impaired function of the cholinesterase enzyme. Administration of sugammadex was indicated with a good response.

At the pre-anaesthesiologic examination, patients were assigned to four classes according to the ASA classification. The comparison of the mean TOF values with the assignment of patients is shown in Figure 3. We found a significant difference between PORC occurrence and patients' ASA classification ( $p = 0.0157$ ). Based on our findings, a higher degree of comorbidity is related to higher probability of lower TOF ratio values. Batistaki et al. [6] showed that patients with ASA III and higher had twice the incidence of PORC as patients with ASA I or II.



**Figure 3. Classification of patients according ASA and means, standard deviations of TOF ratio achieved in these groups.**



**Figure 4. Descriptive characteristics of PORC occurrence in relation to length of surgery.**

Figure 4 depicts the occurrence of PORC in relation to the duration of surgery. Patients were divided into 3 groups according to the length of surgical procedure. Although no differences were statistically significant ( $p = 0.5156$ ), comparing the TOF ratios with the length of the surgery showed evidence that lower TOF ratios occur with intervals of over 120 minutes, thus confirming impact of the length of surgery on the occurrence of PORC [14, 23].

At the time of surgery, atracurium and rocuronium were available at our workplace. Based on the results summarized in Table 1, most doctors seemed to use rocuronium at a ratio of almost 3:1. The main undesirable effects of atracurium are histamine release, bronchospasm, skin seeding and, not least, the inability to use sugammadex to reverse blockade. Our measurements also showed a more frequent occurrence of TOF ratios below 0.9 in patients relaxed by atracurium alone. Atracurium was administered to 40 patients, of which 25 had TOF values  $<0.9$ . Rocuronium was administered to 110 patients, of which a TOF ratio below 0.9 was observed in 50.

**Table 1. Occurrence of PORC depending on the NMBA used.**

NMBA	Total	Repeated administration	TOF ratio $< 0,9$	Average TOF ratio in patients with PORC	p
Atracurium	40	16	25	82,3	0.9203
Rocuronium	110	24	50	83,2	

A statistically significant difference at  $p = 0.0444$  was found in TOF ratios comparing patients without and with use of decurarisation. The frequency of pharmacological decurarisation in these patients is expressed in Table 2. Two forms of decurarisation are applied at our workplace. The so-called 'small decurarisation', which consists of 1.5 mg neostigmine with 0.5 mg atropine, and 'major decurarisation' containing 2.5 mg neostigmine with 1 mg atropine. According to the recommendations, the doses of neostigmine should not be less than 2.5 mg. As Nemes et al. [25] pointed out, the use of neostigmine has been of concern due to its side effects. Among them, undesirable muscarinic side effects and limited ability to reverse even mild neuromuscular blockade in what is considered a "reasonable" time [18, 27] have been associated with deep muscle relaxation [12, 20]. Therefore, it is recommended to administer neostigmine only in cases of some degree of spontaneous recovery or after a shallow blockage (e.g. TOF level 2 or 3) [19]. However, doses of up to 0.015 mg/kg of neostigmine are often sufficient for recovery when the inability to detect TOF diminishes [16, 19]. This was also shown in our study groups. Indeed, in our study most PORC patients required a dose of 2.5 mg neostigmine for block reversal. Nevertheless, up to 9 patients with a TOF ratio  $< 0.7$  were seen, for whom output to normal values was recorded at intervals of 10-15 minutes. A comparison of TOF values in patients with lower and higher doses did not show any significant differences ( $p = 0.8887$ ).

**Table 2. Pharmacological decurarisation.**

	Total	TOF ratio < 0,9 (N)	TOF ratio < 0,7 (N)
neostigmin 1,5 mg	12	3	5
neostigmin 2,5 mg	30	10	9
neostigmin > 2,5 mg	3	1	1
sugammadex	2	0	2

The anaesthesiologists were divided into two groups: with and without certification examination. We wanted to compare the incidence of PORC depending on clinical experience. Mean TOF ratios were 0.84 for medical doctors without certification and 0.82 for those with. Statistical comparison of patients' TOF values did not reveal any differences between groups ( $p = 0.2077$ ). Table 3 provides a closer division of patients by TOF values in relation to doctors' expertise.

**Table 3. The incidence of PORC in patients treated by anaesthetists with and without attestation.**

	Total	TOF ratio < 0,9 (N)	TOF ratio < 0,9 (%)	TOF ratio < 0,7 (N)	TOF ratio < 0,7 (%)
With attestation	92	50	54,4	20	21,7
Without attestation	58	35	60,4	11	18,9

Based on our measurements, we have shown that the incidence of PORC is real and not negligible. The following graph shows the percentage of PORC in the recovery room. In our sample, residual curarisation was present in up to 50% of cases. We compared these results with data from 2010, in which a group of 157 patients showed PORC incidence of 51% in the recovery room (Firmont, 2010). Patients were divided according to surgery into abdominal surgery and others. Similarly, the relationship was monitored between PORC and age and the length of surgery. In our group of patients, we had only one case of postoperative hypothermia with the need for active warming of the patient so this endpoint was not included. Firmont (2010) also excluded patients with hepato- and nephropathy as well as those decurarised in the operating room based on doctors' observations. We have kept these patients in our measurements as they are also at risk of PORC complications. In fact, a total of 47 cases were used for decurarisation. Mostly in the operating room (doctors were aware of ongoing measurements in the recovery room and therefore approached pharmacological decurarisation), but also in the recovery room. Both cases of sugammadex were administered in a convalescence area.

Relaxometry is not mandatory equipment in an anaesthetic device. Although a total of two separate relaxometry devices and one module are available at our workplace, relaxometry during performance was not used in either case during this study. Muscle relaxants have a firm position in anaesthesia. They need to be considered comprehensively, investigating their advantages and adverse reactions. We have shown truly disturbing results: the incidence of PORC in the PACU is up to 50%. We are still within the range indicated in literature, but unfortunately at the upper limit. There are several factors as to why this is the case: from human error on the part of the anaesthesiologist, through lack of communication within the operating team to lack of technical equipment.

The complications of persistent curarisation, such as pneumonia, developed several days after surgery, and were rarely associated with PORC. The only way to prevent this is to monitor muscle relaxation. The anaesthesiologist has indications that predisposes patients to the prolonged effect of muscle relaxants. Age, ASA, length of operation, and low body temperature are risk factors for PORC. However, even in the case of a young patient without comorbidities, it is not possible to objectively exclude residual curarisation without measuring TOF. If this monitor is not applicable, administration of decurarisation is appropriate. In conclusion, it is necessary to say that contemporary evidence-based medicine simply cannot do without monitoring muscle relaxation and without prompt and adequate treatment of postoperative residual neuromuscular block.

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## FDA TIDES Harvest

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### Abstract

A total of 153 new drugs (chemical entities and biologics) approved by the FDA during 2017 to 2019. One of the highlights in 2017 was the number of approved peptides (six). In turn, in 2018, besides one approved peptide there were 2 approved oligonucleotides as well. In 2019, 5 peptides and 2 oligonucleotides were approved. Here, TIDES are analyzed in terms of chemical structure, the synthetic strategy used for their production, source, therapeutic use, and mode of action.

### Keywords:

FDA;  
TIDES;  
SPPS;  
Peptides.

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## Stress and Excessive Fatigue of Healthcare Employees and Medical Errors and their Negative Consequences for the Health and Safety of Hospitalized Patients. with Particular Emphasis on the Legal and Ethical Issues of Medical Personnel Employed Under Civil-Legal Contracts

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### Abstract

This is the first part of a series of case reports. It is a mini review that highlights the pathology in the healthcare sector in Poland after 2011. The authors of the report reveal how the change in employment method (civil-legal contracts) has contributed to the deterioration of safety at the workplace for doctors and the decrease in safety for patients treated by them. The report discusses medical errors made by doctors as a result of stress and fatigue, as well as ethical, legal and criminal consequences of the professional liability of a physician employed under a contract. The authors of the report *de lege ferenda* opt for the introduction of regulations controlling the number of working hour and the length of free time (mandatory rest). This report will present the documented negative consequences of chronic stress and occupational fatigue of medical personnel in Poland between 2014 and 2019, taking into account the provisions of hard law and ethics. The authors of the report will indicate legal and ethical solutions based on Polish legislation that will allow for effective prevention of occupational fatigue and will contribute to improving the working environment of medical staff. They will also show how to effectively counteract possible negative consequences for the health and life of patients and will show pathologies which occur most frequently as a result of fatigue and the human body's response to chronic stress, and which can be subject to criminal law.

### Keywords:

Health at Workplace;  
Stress in Healthcare;  
Pathologies in Healthcare;  
Law;  
Ethics;  
Medical Errors;  
Stress;  
Occupational Fatigue;  
Healthcare Occupational Risk;  
Contract Employment.

## 1. Introduction

The analysis of workplace environment and people's behavior leads to the conclusion that stress and occupational fatigue are primary risk factors that cause development of various pathologies in the work environment [1-4] Many pathologies associated with the effects of a doctor working under long-term stress can be observed in healthcare in Poland. These include, among others, pathologies in the area of legally protected goods, including the protection of human life and health. In particular, exposing a person to the direct danger of loss of life or serious health damage (art. 156 of the Penal Code, art.160 of the Penal Code), causing moderate health damage (art. 157 §1 of the Penal Code) or slight health damage, violation of bodily functions or destabilization of health state lasting no longer than 7 days (art. 157§2 of the Penal Code) [5] This problem is just as harmful and dangerous to medical staff as it is to the patients themselves. However, it is often underestimated and the number of reports on the negative effects caused by stress is still insufficient [6].

This report will present the documented negative consequences of chronic stress and occupational fatigue of medical personnel in Poland between 2014 and 2019, taking into account the provisions of hard law and ethics. The

authors of the report will indicate legal and ethical solutions based on Polish legislation that will allow for effective prevention of occupational fatigue and will contribute to improving the working environment of medical staff. They will also show how to effectively counteract possible negative consequences for the health and life of patients and will show pathologies which occur most frequently as a result of fatigue and the human body's response to chronic stress, and which can be subject to criminal law.

The healthcare sector and hospital services provided to patients require special care and continuous monitoring of the quality of services provided. [7,8,9] So far healthcare in Poland has been focused mainly on developing procedures to improve the treatment process and completely ignored the human factor [10] There is no doubt that stress, fatigue and prolonged working hours (on duty) of medical staff negatively affect their psycho-physical condition and the decisions they make regarding treatment and diagnosis of patients. In such conditions, medical mistakes are made most frequently (by the term "medical mistake" we mean actions that are incompatible with medical knowledge). Consequently, the situation in which human errors occur raises many misunderstandings in terms of criminal law and ethics. Often, medical personnel are also exposed to social ostracism.

Negative experiences and behaviors of healthcare workers (doctors and nurses) caused by chronic stress and occupational fatigue translate into their way of dealing with the patient, their medical errors (diagnostic, therapeutic), including incorrect prescription of hospital drugs which, in consequence, threatens the health and safety of the patient. In such conditions, medical personnel cease to be a guarantee of safety and their behavior becomes a threat to the general public welfare guaranteed by art. 38 and art. 68 point 1 and point 3 of the Polish Constitution [11].

On the basis of discussed cases, we also observe violation of patients' rights and infringement on patients' personal welfare (rights) during hospitalization. Doctors employed under civil-legal contracts do not adhere to the Patients' Rights Act and the Patient Ombudsman [12] Analysis of the discussed cases reveals widespread pathologies in healthcare in area such as: patients' right to consent to the health services being provided, patients' right to information, doctors' right to report adverse effects of medicinal products as well as the necessity to provide a patient, his/her legal representative or guardian, with information about the doctor's intention to cease the treatment.

Doctors as people guarantying patients' safety in a hospital, acting under the influence of chronic stress and obligated by contracts, cease to be guardians of a well-performed medical profession (treatment according to best medical knowledge) [13] Radical errors committed by them because of fatigue (prescribing drugs in lethal doses, diagnostic errors), which may lead to patients' health deterioration, and sometimes even death, cause the medical personnel to be exposed not only to social ostracism, but often also to civil and criminal trials which are a natural consequence of them being asked to take responsibility for their actions.

There is no doubt that the Polish legislation system has indicated effective methods to counteract such problems. The right to safe and hygienic (healthy) working conditions has also been guaranteed (to employees of the health care sector as well) in art. 66 of the Polish Constitution. According to this article, a medical worker has the right to rest and the right to non-working days. The standard maximum working time of a full-time employee in Poland is also specified by statute [14, 15].

The problem, however, arises in the case of medical personnel employed under civil-legal contracts, in which the burden of regulating working time, the right to rest and holidays is the individual responsibility of the person practicing medical profession under the contract signed with a hospital. Authors of this report are of the opinion that the biggest problem with fatigue, chronic stress and burnout and, as a consequence, medical errors made by doctors and nurses most often concern the group of healthcare workers who after 2011 (after the amendment to the Act on medical activity in Poland [15]) are most frequently represented in Polish hospitals. This group is not governed by the rules resulting from the Regulations of the Ministry of Labor and Social Policy on general provisions in the field of occupational health and safety [16] In this group there is also no control over working time and compulsory rest time because civil-legal contract does not specify those and leaves those areas to the medical worker. This is a common employment method in Poland. Medical workers employed under civil-legal contracts constitute a group which itself violates the guaranteed art. 66 of the Polish Constitution. They themselves decide on the consequences of liability and "occupational risk" (probability of adverse events related to their work, resulting in the occurrence of adverse health effects for them and danger factors occurring in the work environment, and also how they perform their work [17]).

## 2. Case Summary

### 2.1. Case I

Hospital with more than 400 beds, hospital with the first degree of reference. Patient admitted to hospital in 2014 during emergency service. Duration of patients' stay in hospital: 2 days.

**Clinical description:** A 63-year-old male patient goes to the hospital with a diagnosed chest pain. The patient is conscious, there is logical verbal contact. Diagnostic and laboratory tests were carried out. ECG examination revealed

a reduction of the ST segment in I, II, aVF, V3-V6. Rest and exertional dyspnoea, cold sweat and peripheral coldness were found. The laboratory tests confirmed the level of cardiac enzyme - Troponin I (Tn I) 0.466 ng / ml (reference range 0.000-0.032). Examination indicates a recent myocardial infarction. Patient admitted to hospital with the diagnosis: gastrointestinal hemorrhage, unspecified.

The doctor who admitted the patient to hospital simultaneously diagnoses an illness, basing his diagnosis on laboratory results. The physician receiving the patient is also his consultant, ordering the admission of the patient to the Liver and General Surgery Clinical Ward.

Admission to the hospital takes place on duty. The patient, who is admitted incorrectly, is transferred to the surgery department. The consequences of misdiagnosis translate into further failure in the treatment of the patient, surgery performed without the patient's consent and administration of a lethal dose of a drug after previous mistakes. The consequence is the patient's death in hospital on the second day of his stay.

**Patient's physician:** According to the patient's source documentation, the attending physician was a man, without doctor's specialty. At that point he had been staying at the workplace for 2 days. He did not reserve sufficient time for rest. He diagnosed the patient himself, performed surgery and prescribed the lethal dose of a drug to the patient after unsuccessful treatment.

**Medical errors:** diagnostic and therapeutic error, surgery performed without the patient's consent, prescribing of a drug in a lethal dose.

#### ***I Diagnostic error:***

A doctor without specialty, admits the patient to the hospital to the Liver Surgery and General Surgery Ward without prior consultation with another doctor. The diagnostic tests carried out showed the diagnosis: myocardial infarction. The patient should be admitted to the cardiology ward. As a result of incorrect diagnosis the patient described as having gastrointestinal haemorrhage - unspecified, is admitted to the surgery department and subjected to surgery without his consent.

#### ***II Therapeutic error:***

At night, the patient is qualified by the receiving physician for the surgery. Classification for the procedure: gastric tumor, gastrotomy. The patient did not express written consent for the surgery - the procedure was performed without patient's consent. After the surgery, a nephrological consultation was ordered. Laboratory tests were carried out and they confirmed the following parameters: Troponin I > 50,000 ng / ml, Potassium 5.2 mmol / l, Creatinine 3.11 mg / dl, Sodium 138.9 mmol / l, Pressure RR 80/36.

Hemorrhagic shock was found during nephrological consultation.

After an unsuccessful surgical treatment and misdiagnosis, and consequently incorrect treatment, the physician committing this diagnostic and therapeutic error ordered the patient a drug at a dose exceeding the pharmacopoeial value (morphini sulfas 88 mg intravenous infusion over 17h, recognized in the literature as a lethal value [18]). As a consequence of wrong decisions, inadequate treatment and the drug administered intravenously, the patient's death was recorded on the second day of his stay in hospital. No adverse drug reactions were reported by doctor despite the statutory obligation [19, 20].

**The final diagnosis indicates:** gastrointestinal disease - unspecified; respiratory failure - unspecified; heart failure - unspecified; unclassified hypovolemic shock.

#### ***2.2. Case II***

Hospital with more than 400 beds, Hospital with the first degree of reference. Patient admitted to the hospital in 2019 in referral mode. Duration of patient stay in hospital: 4 days.

**Clinical description:** A 37-year-old male patient goes to the hospital with a referral to the Gastrology department. Patient previously treated for cancer. Patient admitted with diagnosed pain which has no obvious reason. On the day the patient was admitted to the hospital, laboratory tests were performed: biochemistry, morphology, coagulation, ultrasound and X-ray. On admission, painkillers and third-line antibiotics were prescribed for no reason. On the second day of the patient's stay in the hospital, microbiological urine tests were performed. The presence of Escherichia coli was confirmed.

**Patient's physician:** According to the patient's source documentation, the attending physician was a woman without doctor's specialty. At the point she had been staying at the workplace for 3 days. She did not reserve a proper time for rest. Without proper caution, she prescribed lethal dose of drugs that cross-interact [18].

**Medical errors:** diagnostic and therapeutic error, ordering a drug in a lethal dose.

#### ***I Diagnostic error:***

The patient was not consulted with a specialist before the patient was given a lethal dose of drugs. The doctor did not exercise due care when prescribing medications that entered medium to serious cross-interactions. The patient's family were not informed about the reason for the administration of the drugs and the possible consequences.

#### ***II Therapeutic error:***

The doctor decided to increase the dose of the medicine containing fentanylum as an active substance. 11 mg of this active substance daily along with interacting drugs were given to patient. Those interacting drugs contained active substances such as: fentanylum and metoclopramide hydrochloridum, fentanylum and furosemidum, and morphine sulfas and fentanylum (significant interactions). Drugs were given in the doses exceeding pharmacopoeial values and that led to respiratory depression and, as a consequence, death of the patient [18].

Last day medications were given in interaction and in following doses: Fentanylum 11mg; Morfini sulfas 5mg s.c x 24 hours continuous infusion = 120mg; and 2.5mg s.c morphini sulfas every 4 hours = 15mg. Total dose of drugs administered in interaction: morphini sulfas - 135mg / day; Fentanylum 11mg/day. According to source documents, the patient's condition worsened, respiratory and circulatory arrest occurred.

**The final diagnosis indicated:** post-mortem examinations were abandoned, the cause of death was known to family.

### **3. Results – Treatment sequence**

In these cases all the principles contained in the Constitution of the Republic of Poland, the Act on Patient Rights and the Patient Ombudsman were violated.

A physician's action inconsistent with medical knowledge led to violation of the patient's right to consent to health services, violation of the patient's right to information, violation of the doctor's right to report adverse reactions to medicinal products (after the drug has been ordered in a lethal dose), as well as the violation of the right to provide the patient, his legal representative or guardian with information about the doctor's intention to cease the treatment process.

Mistakes in the treatment process made by a doctor employed under a civil-legal contract violated the patient's legally protected welfare and the rights regarding the protection of human life and health guaranteed by the Constitution of the Republic of Poland. In the analyzed cases, as a result of those actions, the doctors also caused the patients to be exposed to the immediate danger of losing life by performing surgery which was a result of incorrect diagnosis and treatment. This is stipulated in the Polish Penal Code as prohibited (Article 160 of the Penal Code). To perform the act included in art. 160 of the Penal Code there merely needs to be a danger in a situation where the risk is immediate and sufficiently serious, and thus threatens the loss of life or health [21,22] In the discussed situations, the scope of the act being punished in art. 160 of the Penal Code includes the failure to consult the patient with another doctor in order to confirm the correct diagnosis and therapeutic actions undertaken contrary to medical knowledge, threatening the patient's safety. In the discussed cases, the doctors did not properly observe the required caution and consequently caused the patient to be in danger of losing life by giving incorrect diagnosis and treatment. The doctors did not obtain the patients' consent to perform the surgeries, thus failing to comply with the statutory obligation under art. 15 and art. 16 of the Act on Patient Rights and the Patient Ombudsman, and also did not consult the patient's situation with another doctor, which violated the set of principles of professional ethics set out in the Medical Ethics Code of Art. 54 and art. 58 (KEL) [23].

In the legal doctrine, the patient's consent to be provided with medical services is combined with the word autonomy (self-determination). Patient's autonomy is defined as the right to independently decide about his/her rights, and the key element is the ability to express consent to infringement of inviolability and integrity [22] Respecting this right also belongs to the basic duties of medical personnel, regardless of their form of employment, their emotional or psycho-physical condition. Often, however, a doctor operating under a civil –legal contract and under stressful and tiring conditions, taking on the "occupational risk", forgets this basic principle. Additionally, the doctors do not respect (under the influence of chronic stress) the basic ethical standards included in KEL, and also violate the basic principle of *primum non nocere*, which guides their profession.

It is also impossible not to notice that in the aforementioned cases, the principle contained in art. 57 and 74 of KEL (a doctor may not use methods considered harmful by science (art. 57), and moreover, even if a mistake is made, a physician cannot participate in the act of taking a person's life (art. 74) by prescribing a lethal drug dose) was violated. In the analyzed cases administration of a drug in a lethal dose after medical errors proves that the perpetrator has not reversed voluntarily the threat of losing patient's life. Thus, it is possible to objectively attribute the effect belonging

to the characteristics of the subject of the offense. There is a direct link between the breach of precautionary rules by the physician acting as guarantor in relation to the patient under his care, and the resulting effect, which occurred in the form of the recorded death of the patient. In such situations a doctor, not only under conditions of "occupational risk", must take into account the fact that he/she can be responsible for leading to a fatal outcome by prescribing medicines (Article 155 of the Penal Code), since the welfare (i.e. life, health) of a citizen protected by constitutional law was attacked.

Therefore, various ethical questions arise. How far a doctor under chronic stress can go? Stress, fatigue and weakened perception mean that the doctor does not comply with the rules of KEL, and misdiagnosis and mistreatment lead to a situation where the patient's health and life are at risk. Working at night, stress and fatigue generate medical errors that violate the constitutional rights of the citizen, including the right to have their lives respected and protected. However, in a situation where a doctor performs professional duties under a civil-legal contract with deliberate violation of art. 66 of the Constitution of the Republic of Poland and accepts "occupational risk" or causing a situation where a patient's health and life are endangered by an incorrect diagnosis and further incorrect treatment, can that doctor give a patient a lethal dose of a drug? Can such action be justified? Can such action be exempt from punishment?

## 4. Discussion

### 4.1. Ethical Issue

The emerging ethical questions on the basis of the analyzed cases lead to deep reflection - how far a person can go and what can we use as a guide in such situations. In every profession, a person should be guided by a specific ethical code. Especially in medical profession such a code is of utmost importance. *"I will not give anyone a lethal medicine, even if he asks me, nor will I give such advice to anyone. I will not give a woman a miscarriage,"* says Hippocrates, the "father" of medical ethic [24, 25].

It seems that this particular fragment of the oath is causing medical universities of today to depart from the Hippocratic oath. However, who else but Hippocrates should be chosen as a reference point for modern medical ethics, so variable and turbulent? For centuries human life as an inalienable value has remained a value that is fundamental. By rejecting this foundation, the doctor's ethos fundamentally changes and thus questions arise about who has the right to decide about someone else's life, at what stage, with whose consent or perhaps without consent. Without returning to the roots, to the sources, to Greek philosophy and medicine, which was not only a branch of knowledge but also art, it is impossible to solve contemporary dilemmas. Medicine was also a *"paideia"*, which means a method of raising a virtuous man [26].

Pope John Paul II repeatedly referred to this foundation. As early as December 28, 1978, he spoke to members of the Italian Association of Catholic Doctors that abortion and anti-life actions were "contrary not only to Christian, but also to natural morality, as well as to the ethics of the profession expressed in the famous oath by an ancient doctor"[25,26] John Paul II asks whether medicine still remains in the service of people and their dignity, or maybe it is now considered a factor of social life, serving interests of the healthy [27]?

Every human life has the same value and is sacred and therefore one should never kill [28] The doctor's mission is to protect life, human health and to prevent disease. The Code of Medical Ethics talks about it in many points. Article 21 of KEL clearly defines that in the event of a medical mistake or medical error, the physician should take corrective action and notify the patient. It is unacceptable and unethical to conceal a medical error by applying lethal doses of medical substances. Art. 74 of KEL further narrows the ethical attitude of the doctor to the prohibition of participating in any act of taking life, not mentioning hiding mistakes by taking patient's life.

The attitude in which the doctor does not maintain adequate occupational hygiene, for example through fatigue and prolonged stress, has a similar importance in moral evaluation. In no way can the above justify a doctor in his unworthy acts, e.g. prescribing a patient a lethal drug after making a mistake in his/her treatment. Art. 11 of KEL corresponds to this while talking about ensuring adequate conditions for practicing the medical profession without endangering the patient's health or patient's life.

We must not allow doctors, who work continuously for two or three days, to still decide how to treat people while risking a medical mistake. From an ethical point of view, we do not assume purposeful action, but we observe the result of work under the influence of stress and work fatigue. However, there can be no excuse for medical actions aimed at taking life of a sick person, using e.g. lethal doses of a drug.

The Constitution of the Republic of Poland in art. 38 ensures and guarantees protection of human life [11] Therefore, there cannot be any excuse for such actions, even if they result from accompanying circumstances, from direct actions or medical negligence, or from fatigue or occupational stress. Any form of medical personnel's

employment cannot justify their unethical actions in such fundamental issues as health protection or saving human life.

To sum it up, it should be stated that the medical profession, though honorable and garnering great esteem and respect, brings with it many moral dilemmas. However, none of them can lead to a violation of human life whose value is fundamental [29].

#### 4.2. Medical Law Issue

In all of these cases, we can observe there is a violation of the law guaranteed by art. 38, 68 point 1 and point 3 of the Polish Constitution [11]. We can also see violation of the patient's rights and violation of his/her personal rights during hospitalization and the fact that doctors employed under civil-legal contracts do not comply with the Patient Rights Act and the Patient Ombudsman [12]. In particular, there is a violation of the rights of an individual patient using health services in medical entities.

A detailed legal and ethical analysis of these examples, however, reveals widespread pathologies in healthcare in the area of breaking law by healthcare professionals (doctors) employed under civil-legal contracts. Violation of the law by people practicing medical profession under a contractual agreement boils down to the violation of the patient's right to consent to the provision of health services, violation of the patient's right to information, violation of the doctor's right to report adverse effects of medicinal products, as well as violation of the right to provide the patient, his legal representative or actual guardian with information about the doctor's intention to cease treatment process. In addition, this professional group acting under fatigue, stress and overwork due to inadequate caution during work is exposed to criminal liability for acting or failing to act.

Pathologies among health care workers operating under the influence of chronic stress, boil down mainly to violation of the principle to protect human life and health [30]. As a result of perpetual fatigue of health care workers who themselves break art. 66 of the Polish Constitution, we can observe a violation of a citizen's constitutional right which is the legal protection of life as defined in art. 38 of Polish Constitution. The doctor, acting under the influence of fatigue and stress, breaks specific requirements and obligations arising from the standards of the Code of Medical Ethics (KEL), including art. 54 and 58, as well as Art. 57 and 74 [23]. According to art. 58 of KEL, only the attending physician has the right to make decisions related to patient's treatment.

The treatment a doctor employed under civil-legal contract acting under fatigue and forgetting about consultation with another doctor (which would prevent such radical mistakes as ordering a lethal dose of a drug) in fact proves that this treatment is not dictated by a lack of proper knowledge, but is only a consequence of human error which occurs in the absence of due care for occupational health and safety in hospital conditions. It is clear from the cited norms that a doctor may not use methods considered harmful by science (Article 57), and moreover, even if a mistake has been made, the doctor may not participate in the act of taking a sick person's life (Article 74) by prescribing medicine at a lethal dose. This proves directly that failure to comply with the rules of due caution and causing a patient to die, even unintentionally, will result in criminal and legal liability for the doctor for the action taken (Article 155 Penal Code).

The pathologies presented in these cases are mainly the result of chronic fatigue of health care workers and their inadequate care for safe and hygienic working conditions.

Looking at these cases, it cannot be ignored that the lack of healthy and safe conditions at workplace and the violation of the rights guaranteed by the Constitution of the Republic of Poland (Article 66 point 1 and point 2) leads to the violation of other constitutional rights of citizens, who become hospital's patients. This includes article 68 paragraphs 1 and 3 (i.e. the right to health protection, the right to provide special health care to children, pregnant women, the disabled and the elderly). It all puts the health and life of a patient who is under special care of a doctor (acting as a guarantor of safety) at risk.

The presented analyzes of specific medical cases in which adverse events occurred, (e.g. ordering drugs in lethal doses), prove that it is necessary to change legal regulations in the field of controlling the employment of contract staff. Medical errors made by doctors as a result of overwork and acting under stress prove that *de lege ferenda* should be opted for the necessary change in legal regulations. Also more attention should be paid to the working time of medical staff and the need for medical staff to undergo mandatory rest. Opted *de lege ferenda* for following the Austrian model [31] is the introduction of a fine e.g. equaling doctor's one month's salary, for not observing the proper amount of time for rest. This automatically leads to disciplinary action. Therefore, the control of the working time of a contracted physician should, next to the doctor's own discipline, rest with the institution signing the civil-legal contract with the physician performing medical services.

In the opinion of the authors of this report, the introduction of a (*de lege ferenda*) central register of working time of contracted doctors in Poland would reduce the number of rapidly growing pathologies in healthcare which are related to practicing the medical profession with no regard to the abilities of a normally functioning human body. The

principle: *healthy doctor = healthy environment* should guide legislation system regulating the working time of doctors and dentists, as well as nurses and midwives practicing the medical profession in Poland under civil-legal contracts (allowed by the Act on Medical Activity of 2011 - Journal of Law of 2016, item 1638).

It should be noted that in the current legal system, the working time of doctors in Poland is subject to statutory restrictions (resulting from the Labor Code and the Act of 15 April 2011 on medical activities - Journal of Law 2015 item 618, implementing the provisions of Directive 2003/88 / EC of the European Parliament on November 4, 2003) but only when it comes to doctors performing work under an employment contract. A civil-legal contract makes it possible for doctors as well as employers to circumvent the statutorily guaranteed right to an 11-hour rest which should immediately follow an on-call time. This contributes to a decrease in occupational safety and health and consequently generates losses specified in the definition of "occupational risk" in the way the doctors work. This leads to medical errors and endangers safety, health and life of patients treated in Poland.

The law established so far indicates that a doctor employed under a civil-legal contract, by performing medical services guaranteed to a citizen by the Polish state, is responsible for the effects of his fatigue and assumes full responsibility for his actions, including those contrary to medical knowledge, which additionally exposes a doctor to civil and criminal trials and social ostracism.

Physical fatigue and routine cause medical personnel to perform medical procedures without patients' consent and in Polish criminal law this is a separate type of crime (Article 192 §1 of the Penal Code "Whoever performs medical treatment without the consent of the patient, shall be subject to a fine, restriction of liberty or imprisonment for 2 years"). Thus, it is not enough to have just patient consent, but only a non-defective consent to the action clearly indicated by type will allow a doctor to effectively avoid negative effects of his/her actions [32] Also, just causing a risk in a situation where the danger is immediate and sufficiently serious, and thus threatens the loss of life or health, is penalized by the Polish legislator under the provisions of the Penal Code (Article 160 of the Penal Code) in the area of offenses against health for which the person attacking the rights guaranteed by the Constitution of the Republic of Poland, may be responsible. This includes a tired doctor. In the light of the above performing therapeutic procedures without considering one's actions, work beyond the abilities of a human body and fatigue leads to pathology and generates serious medical errors that threaten life and health of treated patients.

In the discussed cases, the attending physician did not consult his or her diagnosis with another physician, did not consult the method of treatment and did not consult the doses of administered medications with a supervisor, which should undoubtedly be considered an act incompatible with medical knowledge and the rules of medical profession.

Attention should be paid to the fact that fatigue, long-term stress and ill-considered actions of health care workers mean that medical personnel in the current legal status and operating under civil-legal contracts are exposed to legal consequences of their actions, both civil and criminal. Undoubtedly, changes in the regulation of the working time of medical staff employed under civil-legal contracts are necessary.

The changes opted for by the authors *de lege ferenda* would allow effective protection of the citizens' health and they would increase the level of safety and work hygiene for medical staff. The issue of fatigue and consequent errors which are being made by the doctors working continuously for many hours (work under civil-legal contracts) illustrates organizational collapse of the healthcare system in Poland.

Improving the working conditions of medical staff, reducing the time of medical and nursing duties, acceptance of treatment procedures by minimum two doctors of the same specialty, as well as the care of the employer for the proper psycho-physical condition of medical staff working under civil-legal contracts, will allow for effective elimination of professional stress, will reduce the number of medical mistakes and will also effectively eliminate ostracism aimed at the exhausted medical personnel, who currently bear the consequences of "occupational risk", as defined in the regulation of the Ministry of Labor and Social Policy in the regulation of September 26, 1997.

However, there is no excuse for the lack of due caution from the doctor and violation of the rights of citizens protected by the Polish Constitution, particularly articles 38 and 68 point 1 and point 3, and in the Act on Patient Rights and the Patient Ombudsman. "The right to protection of life is one of the most important constitutional guarantees, which naturally conditions the existence of all further freedoms and rights. Since human life is a constitutional value, the state is directly called to protect it. The constitution requires the state not only to refrain from introducing regulations allowing the deprivation of human life, e.g. as part of the death penalty, but also to take certain steps to protect this life"[33] In the light of the above, it is unacceptable under Polish law for medical personnel to take actions that violate the constitutional law on the protection of human life. Action that is not in line with medical knowledge and professional medical conduct, and action which is contrary to ethics (such as prescribing lethal doses of drugs after mistakes during treatment process), even under the influence of fatigue and prolonged stress, has legal and criminal consequences for the doctor. Causing a patient to die, either as a result of action or inaction, or by administering a drug, has a specific cause-and-effect relationship, where the cause is the deliberate decision of the doctor to work beyond his physical capacity (assuming occupational risk) and the effect is an incorrect medication



being given and consequently patient's death. In this situation medical personnel must be aware that the burden of legal and criminal liability for the action that is not allowed (offense), even if this is a result of acting under stress or fatigue, will be subject to criminal qualification provided by in Polish criminal law.

Such an act cannot be mitigated because it is contrary to the principles of ethics and harms the citizens' rights protected by the Polish Constitution. Also, taking into account the circumstances i.e. the doctor breaking art. 66 of the Polish Constitution and assuming the burden of criminal liability resulting from deliberately and voluntarily accepted "occupational risk", the punishment provided in the Code may not be subject to any extraordinary mitigation.

#### 4.3. Limitations of case report

Case reports have certain limitations as inherent properties of the design itself and include the following [34]:

- they are regarded as low-level evidence as the observations may be subject to bias,
- lack of ability to be general,
- lack of data that are necessary to calculate the ratio of number of deaths occurring in Poland caused by doctors' medical mistakes,
- lack of comparison or control group to compare outcomes.

Also, the sample is small and describes highly select individuals who may not represent the general population in Poland. Additionally the medical care offered to one patient does not have to produce a similar effect in another patient. Despite these limitations, the authors of this report show serious problem existing in healthcare system in Poland, which changed significantly after 2011 (new legal act pertains to functioning of medical units and doctors' employment conditions). These changes have not been specified precisely in the Polish legal system, and the permission for unlimited doctors' on-call time and the "silent" permission to violate Art. 66 of the Polish Constitution generate serious consequences for the health and life of patients treated in Polish hospitals. In order to generalize the results of this report, it is necessary to conduct further in-depth research based on the analysis of reported criminal proceedings in the "Libra" system.

## 5. Conclusion

In all the analyzed cases, medical errors occurred on duty. Exhaustion, stress and medical procedures performed during doctor's on-call hours led to fatal medical errors. Patients were not treated according to best medical knowledge and professional conduct and the drugs that were prescribed in doses exceeding pharmacopoeial values (lethal doses) resulted in patients' deaths.

This analysis showed that the circumvention of the statutory guaranteed right to 11-hour rest immediately after the end of the on-call time has a negative impact on the safety of patients treated in Poland. This is a serious threat to the health and life of patients treated in hospitals. A doctor practicing medicine under a civil-legal contract, voluntarily deciding to violate art. 66 of the Polish Constitution guaranteeing him/her the right to safe and hygienic working conditions, exposes him/her to criminal liability for medical errors. Stress and occupational fatigue in the conditions of voluntary and deliberate resignation of a physician from his/her constitutional right to rest, does not constitute grounds for leniency for unlawful acts described in art. 156 of the Criminal Code, 157 of the Criminal Code., 160 of the Criminal Code and 155 of the Penal Code as well as in art. 192 paragraph 1 of the Criminal Code.

*De lege ferenda* should therefore be opted for the introduction of provisions, in particular those regulating the procedure for employing doctors under contracts and the introduction of mandatory time for rest in order to improve the safety of treated patients, seems also a necessity. The authors are also of the opinion (opted *de lege ferenda*) that the introduction of a fine e.g. equal to the doctor's one month's salary, for not observing the proper amount of time for rest is necessary. This should automatically lead to disciplinary action. Therefore, the control of the working time of a contracted physician should, next to the doctor's own discipline, rest with the institution signing the civil-legal contract with the physician performing medical services on duty.

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## 7. References

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