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Isoacceptor tRNA in human placenta tissue as assessed with two-dimensional polyacrylamide gel electrophoresis (2D PAGE)

Izoakceptorowe tRNA w tkance ludzkiego łożyska oceniane za pomocą dwukierunkowej elektroforezy w żelu poliakryloamidowym (2D PAGE)

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Abstract. Transfer ribonucleic acids (tRNAs) play a pivotal role in the translation process during protein biosynthesis in the ribosomal system, and also participate in many other processes. It has been observed that changes in cell metabolism are strictly connected with the isoacceptor tRNA population. Human placenta seems to be an adequate model for investigating isoacceptor tRNA population changes due to the morphological and metabolic changes taking place in the course of pregnancy. Placenta tRNA samples were taken by means of phenol-isopropanol extraction and additionally purified by BD-cellulose column chromatography. The labelled and unlabelled tRNA preparations were divided into individual isoacceptors by two-dimensional polyacrylamide gel electrophoresis. Electropherogram analysis suggests that the isoacceptor tRNA population, as pregnancy progresses, shows only small quantitative changes in content of individual isoacceptors, irrespective of pregnancy duration.

Key words: isoacceptors, placenta, transfer RNA

Streszczenie. Trasnportujące RNA odgrywają kluczową rolę w procesie translacji biosyntezy białka w układzie rybosomalnym. tRNA biorą również udział w wielu innych procesach komórkowych. Zaobserowano, że zmiany metabolizmu komórki są ściśle związane z populacją izoakceptorowych tRNA. Ludzkie łożysko jest odpowiednim modelem do badania zmian populacji izoakceptorowych tRNA ze względu na zmiany morfologiczno-metaboliczne zachodzące w przebiegu ciąży. Próbki tRNA łożyskowego zostały uzyskane poprzez ekstrakcję fenolowo-izopropanolową i dodatkowo oczyszczone chromatograficznie na kolumnie z BD-celulozy. Następnie znakowane i nieznakowane preparaty tRNA były rozdzielane na poszczególne izoakceptory z użyciem techniki elektroforezy dwukierunkowej w żelu poliakrylamidowym. Z analizy elektroforegramów wynika, że populacja izoakceptorowych tRNA w miarę trwania ciąży wykazuje jedynie niewielkie zmiany ilościowe zawartości poszczególnych izoakceptorów, niezależnie od czasu trwania ciąży.

Słowa kluczowe: łożysko, transportujące RNA, izoakceptory

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Introduction

Transfer ribonucleic acids (tRNAs) play a pivotal role in the translation process during protein biosynthesis in the ribosomal system. Apart from this function, tRNAs participate in many other processes, e.g. the tRNA isoacceptor for lysine (Lys_3) is a primer for HIV reverse transcriptase; tRNAs form part of the ubiquitin pathway of the protein degradation system, and also in glutamate metabolism [1-3].

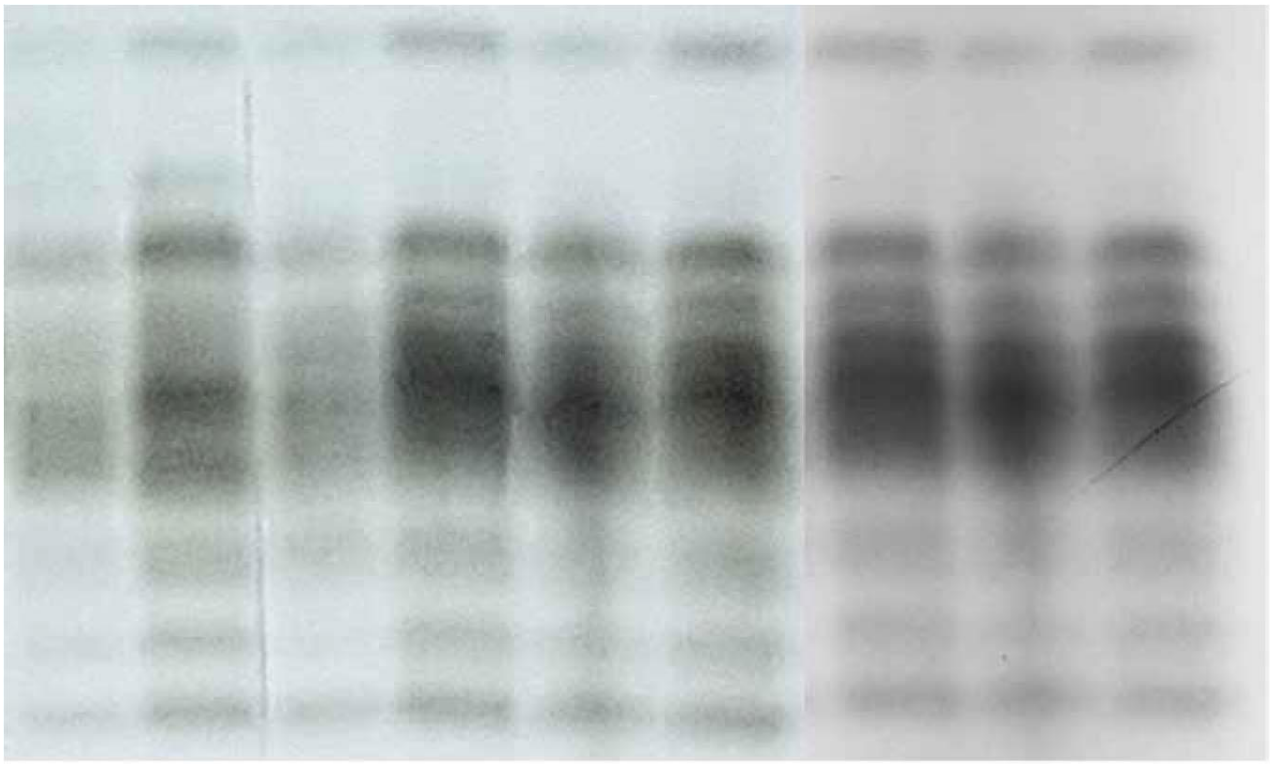

Figure 1. PAGE first dimension electrophoretic patterns of tRNA placental samples from different periods of pregnancy
Rycina 1. Elektroforegram pierwszego kierunku łożyskowych próbek tRNA z różnych okresów ciąży

It was previously observed that highly proliferating cells exhibited changes toward tRNA hypomodification [4]. It is believed that these changes are strictly connected with adaptation of the tRNA isoacceptors population to specific types of metabolism in proliferating tissues [4, 5].

Human placenta tissue seems to be a suitable model for investigation of the tRNA isoacceptor population changes from early to late stage pregnancy. Additionally, it was observed previously that term placenta tRNA exhibits an unusual deficiency in the modified purine base - queuine [6]. Therefore we undertook studies to establish the differences, if any, in the pattern of placental tRNA isoacceptors in the second and third trimesters of pregnancy.

Material

Human placenta tissues from the second trimester of pregnancy were obtained after late spontaneous abortions caused by cervical incompetence, foetus malformations or uterine abnormalities (bicornual uterus). Third trimester placenta tissues were taken after preterm delivery caused by factors other than placental factors (premature rupture of the membrane, uterine preterm contractility) and other factors leading to spontaneous preterm delivery with no placental pathology. All samples were collected by the clinical staff at the Department of Perinatology and at the Department of Gynaecological Surgery, University School of Medicine, Lublin, and at the Department of Obstetrics and Gynaecology at the County Hospital in Bełżyce.

Methods

Immediately after delivery, 10-20 gram samples of placenta tissues were washed in an ice-cold 0.9% sodium chloride solution to remove blood, quickly immersed in liquid nitrogen and stored at -80°C until further processing, but no longer than for 4 weeks. Crude tRNA samples were obtained using the phenol-isopropanol method described previously by Sein et al. [7]. Additional purification by DEAE-52 column chromatography was necessary in order to remove oligonucleotides, DNA fragments and traces of phenol. Total tRNA samples (15 mg) were labelled at the 3' end using nucleotidyltransferase (CCAse - kindly provided by Dr. Pierre Guillemaut, IBMP, Strasbourg, France) and ^{32}P a-ATP (Amersham, United Kingdom). Labelled and unlabelled (50mg) tRNA samples were mixed and the tRNA isoacceptor patterns were obtained using two-dimensional polyacrylamide gel electrophoresis (2D PAGE by methods described by Fradin et al.) [8]. For the

Figure 2. 2D PAGE electrophoretic pattern of tRNA isoacceptors in placenta tissues at 19 weeks
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Figure 5. 2D PAGE electrophoretic pattern of tRNA isoacceptors in placenta tissues at 40 weeks
Rycina 5. 2D PAGE elektroforegram izoakceptorów tRNA w tkankach łożyska z 40. tygodnia ciąży

first dimension, 10% polyacrylamide gel (PAG) in semidenaturating conditions (4M urea) was used, whereas for the second dimension, 20% PAG and 7M urea were used. All electrophoretic procedures were conducted at 4°C and 400 Volts. The duration of electrophoresis was monitored using bromophenol blue and xylene cyanol as markers of tRNA migration. Gels were stained using methylene blue solution and autoradiographed (Fuji film) within 6 to 8 hours at room temperature.

Results and discussion

The first dimension of the electrophoresis was used to obtain approximately 12 fractions located within the 4S area along 6 cm of the gel, for all samples (fig. 1). In the second dimension, for the labelled material nearly 40 well separated sites were obtained, representing particular tRNA clusters of isoacceptors (fig. 2). Using “cold” (unlabelled) tRNA samples, only 25 sites were clearly visible in the gels. These 25 sites were detected by staining with methylene blue, and were completely and fully superpositioned to the labelled tRNA isoacceptors.

No distinct differences were found among tRNA samples taken from particular weeks of gestation. However, it could be observed that minimal quantitative differences (as far as the amount of tRNA isoacceptor was concerned) existed between the tRNA isoacceptors population, irrespective of the advancement of gestation. This probably reflects individual fluctuations in the tRNA patterns. It would appear reasonable to assume that molecular maturation of the placental tissue (in terms of tRNA modification) is established at the beginning of the second trimester of gestation, when trophoblastic tissue has matured in the placenta. After this point, normal metabolism of placenta tissue is already established and independent of ageing. However, further investigations are necessary to extend these observations to the trophoblastic tissue, which is very dynamic in its structural change (maturation), as well as in its functions (oncofetal proteins production, steroidogenesis).

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Comparing the usefulness of FSE and SPGR sequences in the diagnosis of ACTH-secreting pituitary microadenomas

Porównanie przydatności sekwencji FSE i SPGR w diagnostyce mikrogruczolaków przysadki mózgowej wydzielających ACTH

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Abstract. The aim of the study was to assess the efficacy of MR T_1-weighted FSE and SPGR images in the diagnostic evaluation of ACTH-secreting pituitary microadenomas. The study involved 15 patients with Cushing's disease who underwent transsphenoidal surgery for a pituitary tumour, whose histopathological examination confirmed ACTH-secreting adenoma. The preoperative MR study was performed using a 3T scanner with intravenous administration of contrast material. The findings of FSE and SPGR imaging were verified based on surgical locating of tumours. The sensitivity of FSE and SPGR sequences for correct location of the adenomas was 60.0% (9 of 15) and 73.3% (11 of 15), respectively. The positive predictive value was 90% for FSE and 92% for SPGR. Mean tumour size was 3.5 mm +0.9 mm in MR studies and 2.7 mm +0.8 mm intraoperatively. Postcontrast T_1-weighted SPGR images are superior to FSE in the evaluation of pituitary ACTH-secreting adenomas. The inclusion of SPGR should be considered in the standard pituitary MR imaging protocol for patients with hypercortisolemia.
Key words: Cushing's disease, FSE sequence, magnetic resonance, pituitary microadenoma, SPGR sequence

Streszczenie. Wstęp. Celem pracy była ocena skuteczności wykrywania mikrogruczolaków przysadki mózgowej wydzielających ACTH w badaniu rezonansu magnetycznego za pomocą T_1-zależnych obrazów FSE oraz obrazów SPGR. Metody. Badanie wykonano na grupie 15 osób z chorobą Cushinga poddanych przezklinowej operacji guza przysadki mózgowej, u których badanie histopatologiczne usuniętej zmiany potwierdziło gruczolaka wydzielającego ACTH. Przedoperacyjne badanie MR wykonano na 3T aparacie MR z dożylnym podaniem środka kontrastowego. Wyniki obrazowania metodą FSE i SPGR zweryfikowano w oparciu o śródoperacyjną lokalizację zmian. Wyniki. Czułość w zakresie prawidłowej lokalizacji mikrogruczolaka wyniosła 60,0% (9 z 15) dla sekwencji FSE oraz 73,3% (11 z 15) dla sekwencji SPGR. Wartość predykcyjna dodatnia: FSE – 90%, SPGR – 92%. Wielkość zmian wynosiła średnio 3,5 mm ±0,9 mm w badaniu MR oraz 2,7 mm ±0,8 mm na podstawie opisów operacji. Wnioski. Obrazy T_1-zależne SPGR po podaniu środka kontrastowego są skuteczniejsze w wykrywaniu gruczolaków przysadki wydzielających ACTH niż obrazy FSE. Należy rozważyć poszerzenie standardowego protokołu badania przysadki mózgowej o sekwencję SPGR u chorych z hiperkortyzolemią.
Słowa kluczowe: choroba Cushinga, mikrogruczolak przysadki mózgowej, rezonans magnetyczny, sekwencja FSE, sekwencja SPGR

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Introduction

Contrast-enhanced magnetic resonance (MR) is presently the best imaging method in the diagnostics of the pituitary gland [1].

Imaging diagnostics of ACTH-secreting pituitary adenomas still pose a challenge. Most lesions are microadenomas of up to 10 mm in size, and in most cases of 1-3 mm. In an MR examination, the signal and contrast enhancement characteristics in microadenomas are similar to those of normal pituitary parenchyma, which makes identification of the nodules difficult. On the other hand, artefacts may contribute to false-positive results of imaging studies.

A standard protocol of pituitary MRI uses a fast spin echo (FSE) sequence. Average effectiveness of the FSE sequences obtained by the 1.5 T MR system in the detection of pituitary microadenomas in Cushing's disease is 59% [2].

The T_1-weighted spoiled gradient recalled acquisition in the steady state (SPGR) images are characterised by superior tissue contrast. The ability to use thin slices (of 1 mm or of submillimeter thickness) increases the spatial resolution. The short duration of the gradient sequence reduces artefacts due to movement and vascular pulsing, which makes the method well-suited for patients in serious conditions, agitated or non-compliant. Greater power of the magnetic field, combined with gradient-echo, improves the signal-to-noise ratio and homogeneity of the magnetic field [3].

The subject literature provides reports of the superiority of SPGR sequences over FSE in the diagnostics of pituitary microadenomas in Cushing's disease [2, 4-6].

Aim of the study

The effectiveness was assessed of detection of ACTH-secreting pituitary microadenomas using two types of T_1-weighted, contrast-enhanced 3T MR images: classic FSE sequences and SPGR images. The results of the imaging studies were verified based on the intraoperative location of the lesions.

Materials and methods

The study included 15 patients with Cushing's disease who received transsphenoidal surgery for a pituitary tumour, whose histopathological examination confirmed ACTH-secreting adenoma. The study group comprised 13 females (aged 20-56 years old) and 2 males (aged 41 and 45 years old). The surgical procedures were conducted in the Department of Neurosurgery of the Military Institute of Medicine from February to September 2018.

Preoperative diagnostics included hormone tests, inferior petrosal sinus sampling (IPSS) and contrast-enhanced MRI of the pituitary gland.

MR imaging was performed using a 3T system (Discovery 750, GE Medical Systems Milwaukee, WI, USA). The study protocol included two types of T_1-weighted images following intravenous administration of the contrast medium in the frontal plane: FSE and SPGR. The gadolinium contrasting agent Gadovist was used at a dose of 0.01 mmol/kg b.w. (gadobutrol, Bayer Schering Pharma AG, Germany).

The following parameters were used for the T_1-weighted FSE sequences: TR/TE 400/20 ms, matrix: 384 × 224, number of excitations: 4, FOV 16 cm, slice thickness: 2 mm, spacing between slices: 0.3 mm, scanning time: 4:41 min. The parameters used for the T_1-weighted SPGR sequences: TR 350/2.8 ms, flip angle: 90°, matrix: 384 × 192, number of excitations: 4, FOV 16 cm, slice thickness: 2.0 mm, spacing between slices: 0.3 mm, scanning time: 04:32 min.

In 4 patients FSE images were registered first after the administration of the contrast medium, followed by the SPGR images. In 11 patients the images were taken in the opposite order.

Two experienced radiologists independently assessed the T_1-weighted FSE and SPGR images considering the presence size and location of the focal lesion (right side, left side, or midline). In the case of any discrepancy between the assessments, the result was considered inconclusive. Next, the MRI results were compared with the location of the tumour found intraoperatively.

Results

The results are presented in Table 1.

Based on the description of surgical procedures, the intraoperative location of the tumours was established. The size of the microadenoma was available in 7 out of 15 patients, and ranged from 2.0 to 4.0 mm, with a mean of 2.7 mm ±0.8 mm. In other cases the descriptions of operations did not provide the exact size of the lesion.

In the postcontrast T_1-weighted MR images the pituitary tumour was visible as a hypotense focus compared to the surrounding parenchyma (Figures 1 - 2). Suspicious foci were demonstrated in 10 out of 15 patients when using FSE images, and in 12 out of 15 patients when using SPGR sequences.

The FSE and SPGR location of microadenomas was compared with their intraoperative location. The sensitivity of FSE and SPGR sequences for correct location of the microadenomas was 60.0% (9 of 15) and 73.3% (11 of 15), respectively. The difference insensitivity was not statistically significant, at 13.3% (95% CI: 20.1 - 46.7), p = 0.70. A high positive predictive value was obtained: FSE – 90%, SPGR – 92%.

Table 1. Group description. Location and size of tumour according to MR study and surgery
Tabela 1. Charakterystyka grupy badanej. Lokalizacja i wielkość zmian uzyskana w badaniu MR oraz śródoperacyjne

	Sex	Age	Location			Size (mm)	
			FSE	Intraoperative	SPGR	Intraoperative	MR
1	F	31	R	R	R	4	3
2	F	23	L	L	L	3	3
3	F	42	2	R	R	3	2
4	F	56	R	R	R	5	n/d
5	F	40	*	*	L	n/d	n/d
6	F	45	*	L	L	5	n/d
7	F	33	L	L	L	3	n/d
8	M	41	L	L	L	4	3
9	F	49	R	R	R	4	n/d
10	F	20	ML	ML	L	3	4
11	F	35	L	L	L	2	n/d
12	M	45	*	**	R	n/d	2
13	F	27	*	*	ML	n/d	2
14	F	39	R	R	R	3	n/d
15	F	25	L	L	L	3	n/d

n/d – no data, * – isointense lesion, ** – inconclusive image, R – right side, L – left side, ML – midline

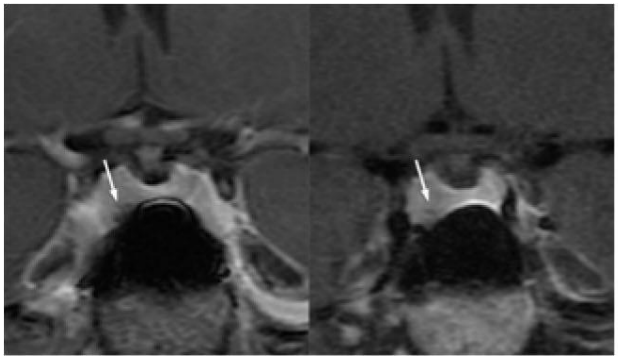

Figure 1. Pituitary MR study, SPGR (on the left) and FSE (on the right) T1-weighted postcontrast images. Microadenoma at the base of pituitary (arrow) is clearly visible on SPGR. The lesion is not obviously separated from the surrounding parenchyma on FSE.

Rycina 1. MR przysadki mózgowej, obrazy T_1-zależne po podaniu środka kontrastowego w sekwencji SPGR (po lewej) oraz w sekwencji FSE (po prawej). Mikrogruczolak u podstawy przysadki (strzałka) jest wyraźnie widoczny w sekwencji SPGR. Zmiana nie wyodrębnia się z otaczającego miąższu w sekwencji FSE.

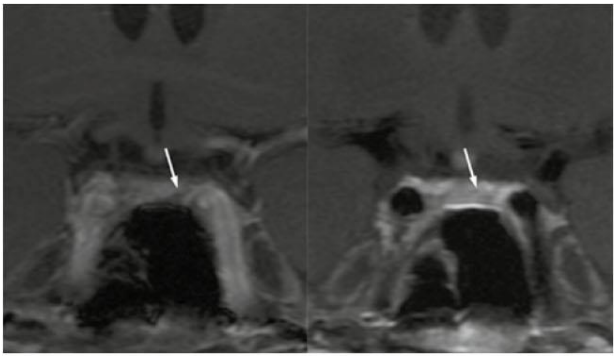

Figure 2. Pituitary MR study, SPGR (on the left) and FSE (on the right) T1-weighted postcontrast images. Microadenoma at the base of pituitary (arrow) is clearly visible on SPGR. Lesion is not obviously separated from the surrounding parenchyma on FSE.

Rycina 2. MR przysadki mózgowej, obrazy T_1-zależne po podaniu środka kontrastowego w sekwencji SPGR (po lewej) oraz w sekwencji FSE (po prawej). Mikrogruczolak u podstawy przysadki (strzałka) jest wyraźnie widoczny w sekwencji SPGR. Zmiana nie wyodrębnia się z otaczającego miąższu w sekwencji FSE.

The results were false negative in 33.3% of cases (5 out of 15) in FSE, and in 20% of cases (3 out of 15) in SPGR.

A single false positive result was observed for both FSE T_1-weighted and SPGR T_1-weighted sequences.

Considering the true positive results (11 out of 15 patients), the mean tumour size in the MRI was 3.5 ±0.9 mm. In four cases it was possible to compare the dimensions recorded in the description of the operation with the tumour size in the MR image. The lesion was 2.8 ±0.5 mm based on the intraoperative estimation, and 3.5 ±0.6 mm based on the imaging test.

Discussion

Transsphenoidal resection of pituitary adenoma is a causative and the best method of treatment in Cushing's disease. Performed by an experienced neurosurgeon, it demonstrates success rates of up to 90% [7]. One of the factors that determine the success of surgical treatment is accurate location of the tumour [8]. It allows planning of surgical access, and reduces the risk of complications due to extensive exploration of the gland, i.e. post-operative pituitary failure and leak of cerebrospinal fluid.

IPSS may be an alternative to MRI in locating the ACTH-secreting tumour [9, 10]. This method helps to determine whether the lesion is located in the pituitary gland or whether it is ectopic. It also allows us to establish the tumour lateralisation in the pituitary gland. However, IPSS does not provide information on the lesion size, or potential invasion of the adjacent structures. The method is also invasive, expensive, associated with a risk of serious complications, and rarely available. Moreover, anatomic variants of the cerebral venous system impair the assessment of tumour lateralisation.

Therefore, the importance of MR imaging in the diagnostics and therapy of patients with Cushing's disease should be emphasised.

Patronas et al. [2] analysed 10 publications with respect to the effectiveness of the MRI examination in the detection of ACTH-secreting adenomas (190 patients in total). The tests were performed on MR scanners with a magnetic field power of 0.5T to 1.5T. A total of 59% of the results were true positive, and 19% were false positive.

Pinker et al. [1] demonstrated the superior effectiveness of a 3T MR scanner to the 1.5T system in the detection of cavernous sinus infiltration by adenoma. The sensitivity for the 3T scanner was 83%, and the specificity was 84%, whereas for the 1.5T scanner the sensitivity was 67%, and the specificity was 58%.

Other studies demonstrated that in 10% of healthy patients, pituitary MR imaging provides false positive results, suggestive of microadenoma [11].

The SPGR sequence was also compared with the dynamic 3T MR system [6, 12, 13], and the superiority of SPGR was demonstrated.

In recent years there have been reports on the use of postcontrast T_1-weighted FLAIR images in the assessment of contrast washout in ACTH-secreting pituitary microadenomas [14].

In the present study, the postcontrast T_1-weighted SPGR images demonstrated a higher sensitivity in the identification of microadenomas than FSE sequences, at 73.3% *vs* 60%, respectively. In both sequences the same slice thickness and similar study times were intentionally used to reduce the effect of volume averaging artefacts and movement artefacts on the results. The difference in sensitivity was not statistically significant, but indicated a higher tissue resolution for SPGR sequences.

The considerable amount of false negative results is noteworthy: 33.3% (5 out of 15) in FSE, and 20% (3 out of 15) in SPGR. In the above cases, the adenomas demonstrated an isointense signal, or the interpretation of the MR images by different radiologists was divergent, despite the fact that the study was performed using the 3T MR system and thin slices.

In one patient the result was false positive in both the FSE sequence and the SPGR.

A comparison of the dimensions of adenomas obtained by MR examination and intraoperatively was possible in only four patients. The mean size of a lesion was 3.5 ±0.6 mm based on the imaging test, and 2.8 ±0.5 mm based on the intraoperative estimation. The tendency to overestimate the size of microadenomas in an MRI examination was visible.

Study limitations included the small size of the studied group, which prevented comprehensive statistical analyses. However, a similar sensitivity of SPGR images in larger study groups was observed by Batista et al. [5] and Patronas et al. [2]: 75% (study group of 30 patients) and 76% (50 patients), respectively. The FSE sensitivity in the quoted publications was considerably lower (21% and 50%), which was probably due to the lower magnetic field power (1.5T), and differences between slice thickness in SPGR (1-2 mm) and FSE (3 mm).

Despite the lack of statistically significant differences, the results of the study suggested the superiority of postcontrast SPGR and FSE T_1-weighted images in the detection of ACTH-secreting pituitary microadenomas, which is consistent with previous reports.

Conclusions

Postcontrast SPGR T_1-weighted images aid in the detection of ACTH-secreting pituitary adenomas more effectively than FSE sequences. The authors of the present study suggest that the standard protocol of pituitary gland assessment should be extended to include SPGR sequences in patients with hypercortisolism.

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Cushing's disease: similarities and differences in the hormonal profiles of pituitary micro- and macroadenomas

Choroba Cushinga: podobieństwa i różnice w profilu hormonalnym mikro- i makrogruczolaków kortykotropowych przysadki

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Abstract. Cushing's disease is a rare but extremely dangerous endocrinopathy caused by corticotroph pituitary adenomas, the size of which in most cases does not exceed 1 cm. The aim of the study was to show clinical and hormonal differences in corticotroph macroadenomas as a rare cause of ACTH-dependent hypercortisolemia. A total of 36 patients with Cushing's disease were analysed (30 females and 6 males, 36.3 years ±12.9). This group included 6 macroadenomas (17%) and 30 microadenomas (83%). There were significant differences in plasma corticotropin (ACTH) concentrations between macro- and microgastrates (178.3 ±69.3 pg/ml and 84.2 ±37.6 pg/ml, respectively, p =0.005), and between the ACTH/cortisol ratio (7.35 ±4.65 and 3.6 ±2.1, respectively, p =0.044) and ACTH/DHEAS (92.2 ±50.7 and 41.7 ±44.4, respectively, p =0.013). However, there were no significant differences between the absolute serum concentrations of cortisol and DHEAS, or changes in cortisol concentrations in the high-dose dexamethasone test. On the basis of the results, differences were confirmed in the hormonal profile between macro- and corticotroph microadenomas; however, the cause of the lower adrenal cortex reactivity to ACTH stimulation in the case of corticotroph macroadenomas requires further investigation.

Key words: corticotroph macroadenoma, corticotropin, cortisol, pituitary adenoma

Streszczenie. Choroba Cushinga jest rzadką, lecz niezwykle groźną endokrynopatią powodowaną przez gruczolaki kortykotropowe przysadki, których wymiar w większości przypadków nie przekracza 1 cm. Celem pracy było wykazanie odrębności klinicznych i hormonalnych makrogruczolaków kortykotropowych, stanowiących rzadką przyczynę ACTH-zależnej hiperkortyzolemii. Przeanalizowano ogółem 36 pacjentów z chorobą Cushinga (30 kobiet i 6 mężczyzn w wieku 36,3 ±12,9 roku). W grupie tej znalazło się 6 makrogruczolaków (17%) i 30 mikrogruczolaków (83%). Wykazano istotne różnice w stężeniu kortykotropiny (ACTH) w osoczu pomiędzy makro- i mikrogruczolakami (odpowiednio: 178,3 ±69,3 pg/ml i 84,2 ±37,6 pg/ml; p =0,005) oraz pomiędzy stosunkiem ACTH/kortyzol (odpowiednio: 7,35 ±4,65 i 3,6 ±2,1; p =0,044) i ACTH/DHEAS (odpowiednio: 92,2 ±50,7 i 41,7 ±44,4; p =0,013). Nie stwierdzono natomiast istotnych różnic pomiędzy bezwzględnymi stężeniami kortyzolu i DHEAS w surowicy ani między zmianami stężeń kortyzolu w teście z dużą dawką deksametazonu. Na podstawie uzyskanych wyników potwierdzono istnienie różnic w profilu hormonalnym pomiędzy makro- i mikrogruczolakami kortykotropowymi. Przyczyna mniejszej reaktywności kory nadnerczy na stymulację ACTH w przypadku makrogruczolaków kortykotropowych wymaga jednak dalszych badań.

Słowa kluczowe: gruczolak przysadki, kortyzol, kortykotropina, makrogruczolak kortykotropowy

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Introduction

Cushing's disease is a hypercortisolism condition caused by an ACTH-secreting pituitary tumour. In most cases, corticotroph adenomas are small tumours of under 10 mm in diameter, but approximately 10-20% of them are larger lesions, so-called macroadenomas, of > 1 cm in diameter. Sometimes they invade adjacent structures, posing a challenge for the operating surgeon. Due to its rare incidence (1-3 million/year), limited data is available on the clinical and hormonal specificity of corticotroph macroadenomas, which - according to the literature reports - are responsible for 10-20% of Cushing's disease cases [1, 2].

Aim of the study

The aim of the study was to compare the hormonal profiles of pituitary corticotroph micro- and macroadenomas, and the response of the adrenal cortex to endogenous ACTH (adrenocorticotropic hormone) stimulation in patients with Cushing's disease preparing for surgical treatment.

Material

The study involved 36 consecutive patients with confirmed Cushing's disease, who were then referred to the Department of Neurosurgery at the Military Institute of Medicine in Warsaw, and operated on by the same surgeon, following the same surgical protocol. The study group included 30 females and 6 males (F:M 5:1), aged 36.3 ±12.9 years old (median: 33.3 years; scope: 16.8 - 57.6 years).

Methods

Cushing's disease was diagnosed based on typical clinical symptoms, as well as elevated serum cortisol concentration, abnormal circadian serum cortisol pattern, elevated plasma concentrations of the adrenocorticotropic hormone, and positive results of a suppression test using high-dose dexamethasone (4x2 mg for 2 consecutive days).

The radiological assessment of the pituitary tumour size was performed by magnetic resonance of the hypothalamus-pituitary system, with the use of a 1.5 T (GE Signa) device, in the sagittal and frontal planes, before and after administration of the contrast medium. Microadenomas were defined as focal lesions whose maximum dimension was less than or equal to 10 mm. Macroadenomas were defined as lesions of over 10 mm in at least one dimension.

Table 1. Relationship between concentration of cortisol (µg/dl) and ACTH (pg/ml) and pituitary adenoma size in magnetic resonance imaging (see the text)
Tabela 1. Zależność pomiędzy stężeniem kortyzolu (µg/dl) i ACTH (pg/ml) a wielkością gruczolaka przysadki w obrazowaniu metodą rezonansu magnetycznego (opis w tekście)

Hormone \ Tumour size		Microadenoma or inconclusive MR	Macroadenoma (tumour > 1 cm)	p
Cortisol (µg/dl)	N	30	6	0.702
	Mean	25.7	26.98	
	±SD	7.74	5.4	
	Median	24	28.25	
ACTH (pg/ml)	N	30	6	0.005
	Mean	84.21	178.33	
	±SD	37.57	69.31	
	Median	81	179	
ACTH/cortisol	N	30	6	0.044
	Mean	3.63	7.35	
	±SD	2.064	4.65	
	Median	2.78	6.27	
DHEAS (ng/ml)	N	30	6	0.777
	Mean	3410.93	2774.8	
	±SD	1990.54	1917.62	
	Median	2970	3492	
ACTH/DHEAS	N	30	6	0.013
	Mean	41.69	92.2	
	±SD	44.4	50.73	
	Median	25.02	75.89	

ACTH concentrations were determined by immunoradiometric assay (IRMA), using an ELSA-ACTH kit, CisBio International, France. The analytical sensitivity of the test was 2 pg/ml. Morning plasma ACTH concentrations of 10-60 pg/ml were adopted as normal values.

Cortisol concentrations were determined by electrochemiluminescence immunoassays (ECLIA) with the use of an Elecsys 2010 kit by Roche Diagnostics, Switzerland. The analytic sensitivity of the test was 0.02 µg/dl. Normal morning cortisol concentrations were defined as 6.2 - 19.4 µg/ml. The same method was used to determine concentrations of dehydroepiandrosterone sulfate (DHEAS). The analytic sensitivity of the test was 3 µg/dl (0.08 µmol/l).

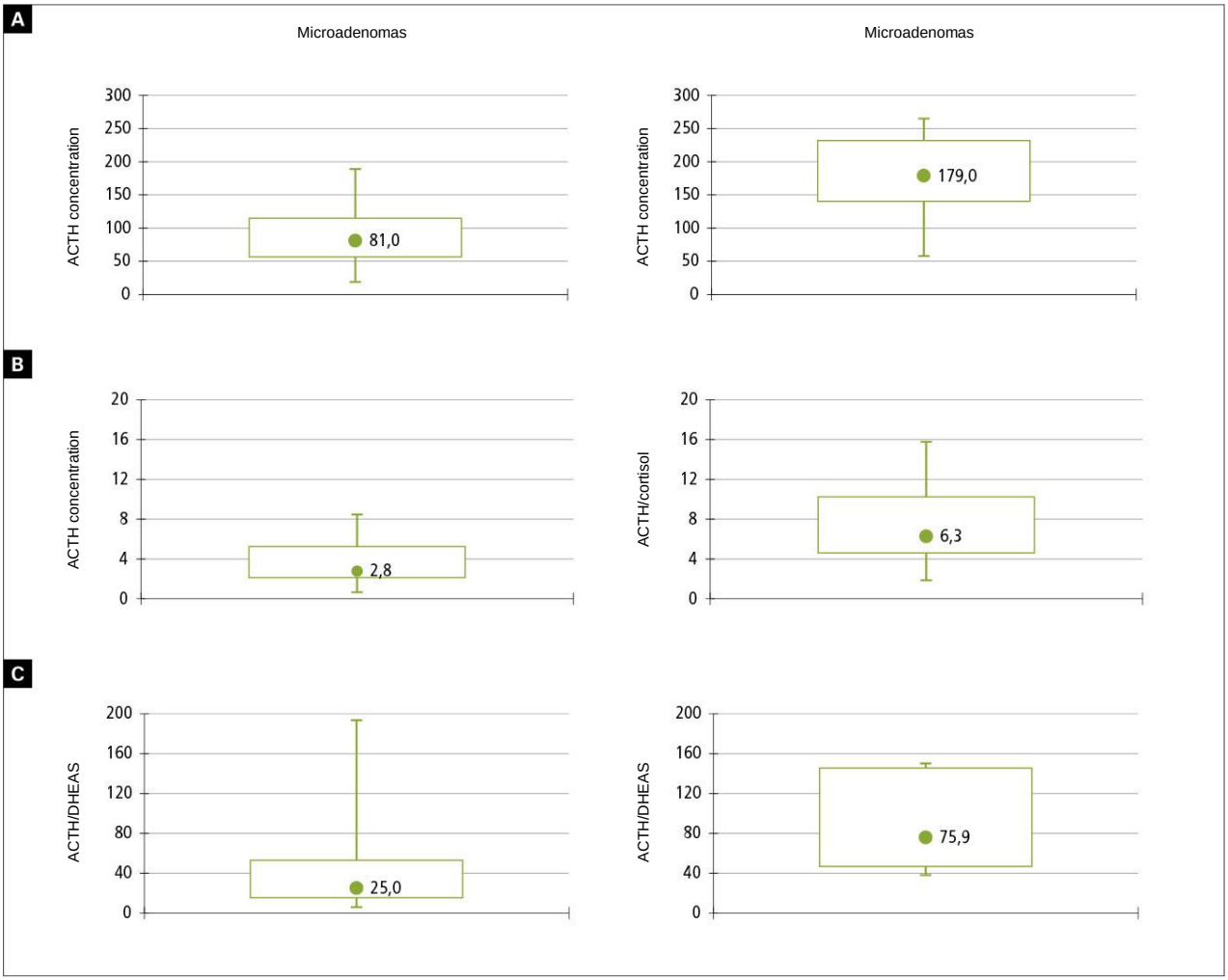

Figure 1. Frame charts showing the comparison of hormonal determinations depending on the size of the pituitary adenoma in the MR study. Range (min–max) is presented; 25 and 75 percentile (frame); inside the frame – middle value (median). **A.** ACTH levels and size of pituitary adenoma in MR imaging (p =0.005). **B.** ACTH/cortisol ratio and size of pituitary adenoma in MR imaging (p =0.044). **C.** ACTH/DHEAS ratio and size of pituitary adenoma in MR imaging (p =0.013).

Rycina 1. Wykresy ramkowe obrazujące porównanie oznaczeń hormonalnych w zależności od wielkości gruczolaka przysadki w badaniu MR. Przedstawiono zakres (min–max); 25. i 75. centyl (ramka); wewnątrz ramki – wartość środkowa (mediana). **A.** Stężenia ACTH a wielkość gruczolaka przysadki w obrazowaniu metodą MR (p =0,005). **B.** Stosunek ACTH/kortyzol a wielkość gruczolaka przysadki w obrazowaniu metodą MR (p =0,044). **C.** Stosunek ACTH/DHEAS a wielkość gruczolaka przysadki w obrazowaniu metodą MR (p =0,013).

Results

The group of patients involved 6 patients with pituitary corticotroph macroadenoma and 30 patients with microadenoma (17% and 83%, respectively). In both groups plasma ACTH concentrations and serum cortisol levels were analysed to demonstrate potential differences according to the size of the pituitary corticotroph tumour. The t-Student test did not demonstrate any significant differences in mean cortisol concentrations between the subgroups (p = 0.702). The non-parametric Mann-Whitney exact test revealed a significantly elevated ACTH concentration in the group of patients with pituitary macroadenoma (p = 0.005), and confirmed that the ratio ACTH - cortisol concentration ratio was higher in pituitary macroadenomas, and that the difference was statistically significant (p = 0.044).

The analysis of DHEAS also did not demonstrate any differences between microadenomas and macroadenomas (p = 0.777). However, the comparison of the ACTH/DHEAS ratio revealed a significant difference between those patients with pituitary microadenomas on one hand and patients with corticotroph macroadenoma on the other (p = 0.013). The detailed results are presented in Table 1 and Figure 1.

Table 2. Relationships between preoperative cortisol concentrations in the dexamethasone test (HDDST) and pituitary tumour size in the MR study: comparison of micro- and macroadenomas
Tabela 2. Zależności między przedoperacyjnymi stężeniami kortyzolu w teście z deksametazonem (HDDST) a wielkością guza przysadki w badaniu MR: porównanie mikro- i makrogruczolaków

Tumour size in MR image		Baseline cortisol concentration (µg/dl)	Cortisol in the dexamethasone suppression test (HDDST)					
			Absolute values in µg/dl		Absolute difference (Δ) in µg/dl		Relative difference (Δ%) (% of the baseline value)	
			Day 2	Day 4	Day 2	Day 4	Day 2	Day 4
Microadenoma	N	30	30	30	30	30	30	30
	Mean	25.70	12.03	6.85	13.67	18.85	45.89	26.51
	±SD	7.74	8.19	7.15	7.43	8.96	24.54	24.55
	Median	24	9.7	3.75	13.21	17.96	41.47	14.84
Macroadenoma	N	6	6	6	6	6	6	6
(Tumour >1 cm)	Mean	26.98	12.89	6.12	14.09	20.86	50.5	23.46
	±SD	5.40	5.37	4.58	8.25	7.22	23.74	17.39
	Median	28.25	13.55	4.81	12.95	22.6	54.91	18.91
p		0.520	0.493	0.725	0.918	0.548	0.725	0.852

Analogous calculations were conducted for the dexamethasone suppression test (HDDST). The non-parametric Mann-Whitney exact test compared absolute values of cortisol concentrations on days 2 and 4 of the test, as well as absolute differences (A) and relative differences (A%) between the baseline cortisol and the values measured on days 2 and 4 of the dexamethasone test. No statistical significance was demonstrated between the group of pituitary corticotroph microadenomas and macroadenomas (Table 2).

The qualitative analysis revealed reduced serum cortisol concentrations on day 4 of the pre-operative dexamethasone test (HDDST) in 25 out of 30 patients in the group of patients with microadenomas and inconclusive MR images, which constituted 83.3%, and in 5 out of 6 patients with corticotroph macroadenoma, which was also 83.3% (p = 1.0 in the Fisher's test).

Discussion

The present study demonstrated statistically significant differences in pre-operative hormone assays between pituitary micro- and macroadenomas. Significantly higher ACTH concentrations in the group of macroadenomas, with similar concentrations of cortisol and DHEAS, may indicate a weaker reactivity of the adrenal cortex with regard to cortisol and androgen secretion in response to excess adrenocorticotropic hormone. These observations are further supported by the statistically significant differences between the ACTH/cortisol ratio and ACTH/DHEAS ratio in both subgroups. This may be due to the changed structure of the ACTH molecule secreted by macroadenomas, which exerts a weaker biological effect in the adrenal cortex [3]. However, the different biochemical profiles of micro- and macroadenomas does not appear to result from significant differences in biological features of the tumour, as it has been demonstrated that corticotroph adenomas, regardless of their size, are monoclonal [4, 5]. This means that, apart from MEN-1 syndrome, they originate from a spontaneous mutation that leads to an uncontrollable proliferation of mutated corticotroph cells. The differences between the activity of Ki-67 proliferative antigen observed between microadenomas and invasive macroadenomas may reflect the difference between the mutation resulting primarily in excessive ACTH secretion (and a limited progression of the lesion), and the mutation that leads to uncontrollable tumour growth (with less pronounced functional disorders) [4-7].

The present study did not confirm the observations made by Woo et al. and Cannavo et al. regarding the higher "resistance" of pituitary macroadenomas to dexamethasone suppression [3, 6]. The analysis of serum cortisol concentrations obtained in the two-day dexamethasone test did not reveal a significant difference between micro- and macroadenomas. This finding contradicts the suggestion that macroadenomas in Cushing's disease demonstrate a higher degree of autonomy, and are less susceptible to diagnostic suppression with dexamethasone [3].

Conclusions

Corticotroph macroadenomas demonstrate a different secretion profile, characterised by a higher production of adrenocorticotropic hormone compared to micro-adenomas.

However, ACTH secreted by macroadenomas is less biologically active with respect to stimulation of cortisol and dehydroepiandrosterone sulfate production by the adrenal cortex.

The size of pituitary corticotroph adenoma does not affect the results of the quantitative and qualitative assessment of the dexamethasone suppression test performed in the diagnostics of Cushing's disease.

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Cytometric analysis of transbronchial lymph node biopsy in patients with lung sarcoidosis

Analiza cytometryczna materiału z biopsji transbronchialnej węzła chłonnego u chorych na sarkoidozę płuc

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Abstract. Lung sarcoidosis is a generalized granulomatous disease with an unknown aetiology, often accompanied by mediastinal lymphadenopathy. One of the methods helpful in the differential diagnosis of sarcoidosis is the cytological evaluation of the material originating from the respiratory tract, and determining the ratio of helper T cells (CD4) to suppressor/cytotoxic T lymphocytes (CD8). The aim of the study was a cytometric evaluation of the material from the transbronchial lymph node biopsy, taken using the EBUS-TBNB technique ("transbronchial node biopsy"), and an assessment of its usefulness in the diagnosis of patients with lung sarcoidosis. The diagnosis of sarcoidosis was made in 12 of the 23 patients with mediastinal lymphadenopathy. In patients with pulmonary sarcoidosis an increased percentage of CD8+ lymphocytes was found significantly more often (19.34% ±7.98%, median 19.8%) in the examined material. However, symptoms of arthritis were significantly more frequent in patients with an increased percentage of CD3+ T lymphocytes (64.49% ±11.9%, median 65.85%). The study showed that the flow cytometry of cytological material with TBNB-EBUS in conjunction with clinical data is useful in the diagnosis of lung sarcoidosis.

Key words: endobronchial ultrasound, flow cytometry, lymphocytes CD4/CD8

Streszczenie. Sarkoidoza płuc jest uogólnioną chorobą ziarniniakową o nieznanej etiologii, której często towarzyszy limfadenopatia śródpiersia. Jedną z metod pomocnych w diagnostyce różnicowej sarkoidozy jest ocena cytologiczna materiału pochodzącego z dróg oddechowych oraz oznaczenie w nim stosunku limfocytów T pomocniczych (CD4) do limfocytów T supresorowych/cytotoksycznych (CD8). Celem pracy była ocena cytometryczna materiału pochodzącego z biopsji transbronchialnej węzła chłonnego, pobranego z użyciem techniki TBNB-EBUS, oraz ocena jej przydatności w diagnostyce chorych na sarkoidozę płuc. Rozpoznanie sarkoidozy ustalono u 12 z 23 badanych chorych z limfadenopatią śródpiersia. U chorych na płucną postać sarkoidozy w badanym materiale istotnie częściej stwierdzano zwiększony odsetek limfocytów CD8+ (19,34 ±7,98%, mediana 19,8%). Objawy zapalenia stawów występowały natomiast istotnie częściej u chorych ze zwiększonym odsetkiem limfocytów T CD3+ (64,49 ±11,9%; mediana 65,85%). Wykazano, że cytometria przepływowa materiału cytologicznego z TBNB-EBUS w powiązaniu z danymi klinicznymi jest przydatna w diagnostyce sarkoidozy płuc.

Słowa kluczowe: cytometria przepływowa, limfocyty CD4/CD8, ultrasonografia wewnątrzoskrzelowa

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Introduction

Lung sarcoidosis is a generalised granulomatous disease of unknown aetiology. It is characterised by enlarged mediastinal lymph nodes and diffused lesions in the lungs. It may also involve other organs, e.g. eyes, liver or skin.

The disease primarily affects young people, aged 20-29 years old, and the second peak is observed in women over 50 years old.

Sarcoidosis is diagnosed based on a clinical examination, imaging tests, and histopathological examination, which should demonstrate the presence of non-caseous granulomas in the invaded tissues. It is necessary to exclude other granulomatous diseases and a local sarcoid reaction [1, 2].

Sarcoid granulation tissue is formed via numerous immunological mechanisms. An unknown antigen is ingested by macrophages or dendritic cells, and then presented via the human leukocyte antigen (HLA) system to the T lymphocyte receptors (mainly CD4+). Cell aggregation is due to their redistribution from the blood, and local proliferation. Cytokines such as interleukin-2 (IL-2), interleukin-15 (IL-5) and interleukin-16 (IL-16) participate in these processes. Sarcoid granulation tissue is composed of epithelioid cells and multinucleated giant cells, but CD4+ lymphocytes predominate; individual CD8+ lymphocytes and occasional B lymphocytes are also found [2, 3].

Previously, one of the diagnostic methods used in the differential diagnosis of mediastinal lymphadenopathy was bronchoalveolar lavage (BAL). BAL is a method of obtaining cellular and non-cellular material from the surface of the epithelium lining the peripheral airways, i.e. the bronchoalveolar space. The assessment of the CD4+ and CD8+ lymphocyte rate, including the CD4/CD8 ratio, is useful. In special cases when lymph node involvement is suspected, markers of B lymphocytes may also be used.

The cellular composition of the BAL material is not pathognomonic for sarcoidosis. The total cell count may be normal, or slightly elevated [4].

Due to the emergence of new diagnostic methods, it is also possible to obtain material via cytological biopsy of a mediastinal lymph node. The cellular composition of material collected through EBUS-TBNB (transbronchial needle aspiration endobronchial ultrasound) from a mediastinal lymph node has been assessed in few publications [5].

In addition, there are no studies evaluating other elements of the node, or their importance for the assessment of advancement of sarcoidosis symptoms.

Aim of the study

The aim of the study was to assess the usefulness of flow cytometry of a lymph node biopsy in the diagnostics of lung sarcoidosis.

Material and method

The study involved 23 patients (10 females and 13 males), aged 42 ±15.3 years old, with suspected 1st or 2nd degree sarcoidosis, based on a topographic examination of the thorax. Löfgren's syndrome was found in 6 patients of this group. The patients received an endoscopic examination of the bronchial tree using an OLYMPUS endoscope (Olympus UC260FW, Olympus Co Ltd., Tokyo, Japan). Local anaesthesia of the oral cavity and pharynx (10% lidocaine solution) as well as the bronchial tree (2% lidocaine solution) was applied, as well as analgosedation including intravenous administration of 2.5 mg of midazolam, 0.05 mg of phentanyl and 0.5 mg of atropine.

The nodal station was selected based on the analysis of the topographic examination. The final choice was made by the operating surgeon, who selected a node from the following groups: upper paratracheal (group 2), lower paratracheal (group 4), subcarinal (group 7), and interlobar (group 11). The selected nodes were over 1 cm long in the short axis, and demonstrated an atypical sonographic image (hypoechogenicity, non-echogenic hilum).

A real-time TBNB EBUS transbronchial biopsy of the mediastinal lymph nodes was performed, using a G 21-22 Olympus needle. The material for histopathological examination was fixed in 96% alcohol (cytology), or 10% formaldehyde (cytoblock). The material for cytometric analysis was preserved in 3 ml of 0.9% NaCl solution. 100 µl of the studied cellular suspension was placed in cytometric Falcon tubes, and monoclonal antibodies added, in the amount recommended by the manufacturer. The tubes were used for the acquisition and analysis using a FACS Canto II flow cytometer, DIVA 8.0 software and INFINICYT data analysis programme. To label the cells, the following antihuman murine antibodies were used: CD4 FITC, CD5 PE, CD3 PerCP-Cy5-5, CD19 PE-Cy7, CD8 APC, CD16, APC-H7, HLA-DR, V450,CD45, V500, CD79b PerCP-Cy5-5, CD10 APC, CD38 APC-H7, CD20 V450 (Becton Dickinson), and to assess the clonality of the B lymphocyte immunoglobulin light chains, lambda FITC and kappa PE antibodies (Dako) were used.

The following parameters were determined in the study material: percentage of leukocytes and individual lymphocyte subpopulations, immunophenotype of B lymphocytes, and percentage distribution of immunoglobulin light chains in the B lymphocytes (CD4, CD8, CD19, NK, monocytes, granulocytes, light chains).

Table 1. Cell distribution in cytometry (mean ±SD)
Tabela 1. Rozkład komórek w cytometrii (średnie ±SD)

№	Parameter	Percentage distribution (%) ±SD
1	Lymphocytes	84.72 ± 17.351
2	CD4+	43.122 ± 12.99
3	CD8+(%)	13.95 ± 5.65
4	CD4/CD8	3.57 ± 1.88
5	B lymphocytes CD19+	25.01 ± 14.64
6	NK lymphocytes CD3-CD16+	2.49 ± 1.59
7	Monocytes (%)	2.76 ± 3.71
8	Granulocytes (%)	12.33 ± 15.73
9	Kappa chains (%)	53.34 ± 13.55
10	Lambda chains (%)	40.37 ± 10.77
11	k/l	1.29 ± 0.42

Statistical analysis of the results

The analysis involved basic descriptive statistics: means, medians and standard deviations for individual cells obtained from the lymph node biopsy.

The Mann-Whitney U-test was used to demonstrate the differences in node cellularity depending on the organ involved by the sarcoidosis.

Results of the study

Sarcoidosis was confirmed in 12 out of the 23 patients. The distribution of cells based on the cytometric analysis is presented in Table 1.

The results of cytometry were compared to the clinical picture of the patients. More frequent occurrence of a higher number of CD8+ lymphocytes (19.34 ±7.98%; median 19.8%) was demonstrated when lung parenchyma was involved (CTthor+). The difference was statistically significant ($p < 0.05$) (Fig. 1).

A higher number of T lymphocytes CD3+ (64.49 ±11.9%; median 65.85%) was observed more frequently in patients with the symptoms of arthritis (J+). The difference was nearly statistically significant ($p = 0.0545$) (Fig. 2).

Discussion

Differential diagnosis of sarcoidosis is based on the clinical picture, radiological image of the thorax, and confirmation of the presence of granulomas from epithelioid cells without necrosis [2]. The recommended diagnostic methods include endobronchial ultrasound-guided transbronchial needle biopsy (EBUS TBNB), which is a highly efficient diagnostic method whose sensitivity is 88-95%, and its predictive value for negative results is 86-95% [1].

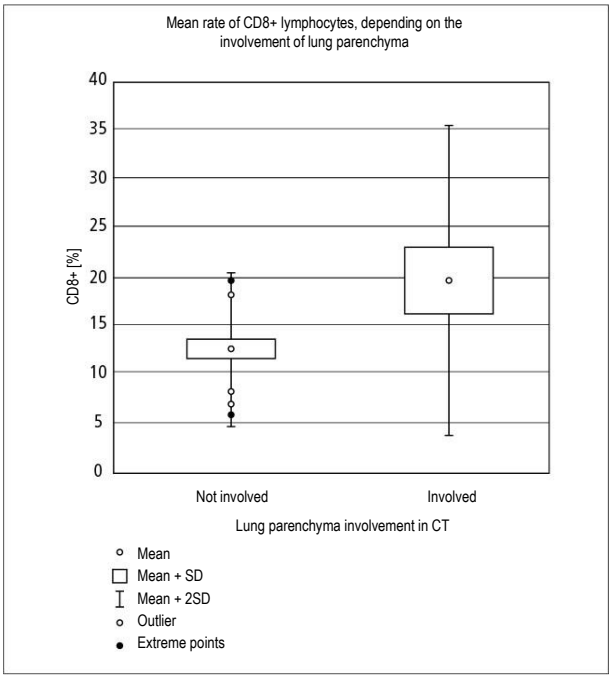

Figure 1. Percentage of CD8+ lymphocytes depending on pulmonary lesions, $p < 0.05$
Rycina 1. Odsetek limfocytówCD8+ w zależności od zmian płucnych, $p < 0,05$

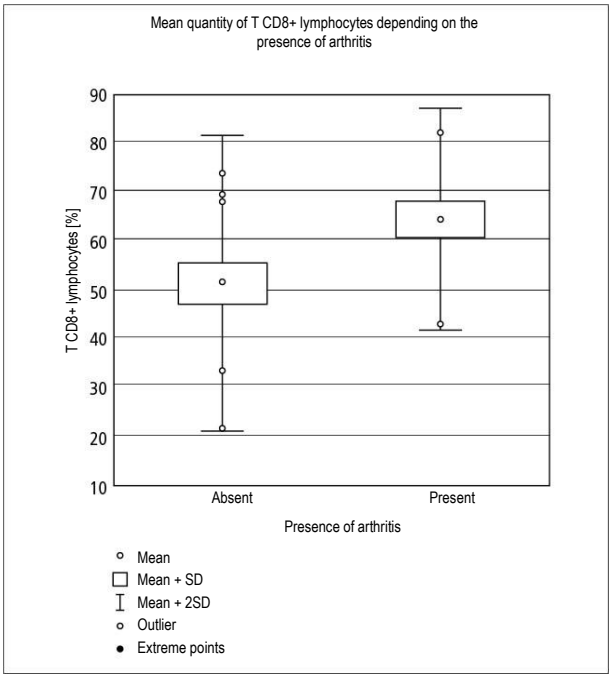

Figure 2. Percentage of CD3+ T lymphocytes depending on clinical manifestation of arthritis, $p = 0.0545$
Rycina 2. Odsetek limfocytów T CD3+ w zależności od obrazu klinicznego zapalenia stawów, $p = 0,0545$

Such high specificity and sensitivity applies both to the diagnostics and differentiation of neoplastic diseases (lung cancer metastases to lymph nodes), and to the diagnostics of interstitial diseases. The procedure is associated with a low risk of complications. The method is more effective than a blind biopsy of the mediastinal lymph nodes performed after the analysis of a tomographic image of the thorax. The diagnostic effectiveness of a blind biopsy is 73.1%, whereas the effectiveness of EBUS-TBNB is 95.8% [6, 7].

In cases in which the diagnosis could not be confirmed histopathologically, clinical observation of the symptoms is required. Diagnosis based on symptoms is acceptable in the case of acute sarcoidosis in the form of Löfgren's syndrome, characterised by increased body temperature, arthritis, erythema nodosum, and hilar lymphadenopathy in a thoracic imaging test.

The EBUS-TBNB technique also allows differentiation between sarcoidosis and a neoplastic process, whose clinical and radiological presentation can be similar, and which can occur simultaneously. Therefore, the diagnostic methods are selected in a way that enables the establishment of a precise diagnosis in the case of the negative results of the histopathological examination, saving the patient from the need for an operation, such as a surgical lung biopsy [8].

Bronchoalveolar lavage and analysis of cellularity in the aspirate have an established position in the diagnostics of interstitial lung diseases. The demonstration of a CD4/CD8 ratio of >3.5 in the bronchial aspirate, together with the clinical data, justifies the diagnosis of sarcoidosis. According to the literature data, the effectiveness of this method ranges from 40 to 60% (sensitivity of 52%, specificity of 94%). However, there is a group of patients with sarcoidosis confirmed in a surgical lung biopsy, whose CD4/CD8 ratio was approximately 1 [9].

There are also reports relating a high CD4/CD8 ratio in the bronchial aspirate to pronounced clinical and radiological signs of sarcoidosis [8].

Flow cytometry of the cellular material from fine-needle biopsy provides an interesting alternative for BAL. This method may be one of the earliest elements in the differential diagnostics of lymph node neoplasms or metastatic lesion in the mediastinal lymph nodes [10, 11].

Flow cytometry allows us to analyse several morphological and immunophenotypic parameters at the same time. It is a fast method, offering analysis of the immunophenotype with the use of more monoclonal antibodies (MoAg) than in immunohistochemical tests, which enables a simultaneous analysis of at least 4 antigens in one assay, as well as a comparison of the relative density of antigens on the neoplastic cells and on T or B lymphocytes in the suspension [12, 13]. This method is also very important for patients with clinical conditions or contraindications, as well as in those cases where the site for surgical biopsy is difficult to access, such as the retroperitoneal space or anterior mediastinum. Flow cytometry of the material from an aspiration biopsy also enables us to exclude quickly and unambiguously the diagnosis of non-Hodgkin lymphoma (NHL) in small cell cancers (sarcomas, small cell carcinomas) [14].

The CD4/CD8 ratio determined by flow cytometry of the sample obtained from a biopsy of a mediastinal lymph node is higher (in 52% of patients) than in the material from BAL (in 45% of patients) in patients with sarcoidosis. It indicates a higher sensitivity of this method when analysing a lymph node sample. In addition, the CD4/CD8 ratio is different, and can be considerably higher relative to the radiological stage of sarcoidosis [5].

In the study group a higher lymphocyte count was observed in patients with pronounced clinical (arthritis) and radiological (involvement of lung parenchyma) symptoms. It appears that cytometry of the biopsy may play a role in the assessment of the pathomechanism of sarcoid lesions, and the clinical picture of the disease. Conclusions should be drawn carefully, as various opinions are available in the literature; e.g. Ruiz et al. concluded, having analysed material from BAL and lymph node samples, that the CD4/CD8 ratio does not provide a reliable differential diagnosis [15]. Such a discrepancy may be due to the laboratory methods used, although, according to the authors, it is primarily due to the improper selection of the biopsied lymph node. Lymph nodes with sarcoid granulation tissue are enlarged, and their ultrasound image is characterised by a non-echogenic hilum and hypoechogenic structure. It should be emphasised that during the examination of patients with mediastinal lymphadenopathy and suspected sarcoidosis, some lymph nodes may demonstrate an abnormal ultrasound image (as described above), and others may be enlarged, but structurally normal.

Sonographic characteristics of a lymph node that are highly suggestive of metastatic lesions include: heterogenic pattern, round shape, clear margin and absence of central hilar structure [7]. In the assessment of the lymph node structure during EBUS, vascular models may also be used with the Doppler ultrasound. Their division takes into account the size of the flow, from limited to high. The test detects pathological (neoplastic) lesions with high specificity [16].

A sonographic model of a lymph node in interstitial lung diseases has not been developed yet. The authors of the above mentioned study use certain characteristic abnormalities (e.g. absence of hilar structures) in the lymph node to indicate the location of the lymph node level to be biopsied.

The usefulness of other elements of a lymph node, determined through cytometry in the diagnostics of sarcoidosis, has not been confirmed, but their importance is significant in the diagnostics of neoplastic diseases, particularly lymphomas [17].

Conclusions

The emergence of endobronchial ultrasound studies opened a new chapter in interventional pulmonology. It allows targeted biopsies to be conducted of mediastinal lymph nodes with a high safety profile. The resulting lymph node biopsy can be used not only in histopathological assessments, but also in flow cytometry. This method allows the determination with high sensitivity the type of lymphocytes in the lymph node. It can also be applied in the differential diagnostics of mediastinal lymphadenopathy, e.g. in patients with suspected sarcoidosis, in particular when the clinical picture is atypical. The progress in the development of cellular markers of the lymph node lymphocytes will facilitate and accelerate the diagnostics of lymphadenopathy and mediastinal tumours.

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Progress and perspectives in the surgical treatment of thermal burns

Postępy i perspektywy w chirurgicznym leczeniu oparzeń termicznych

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Abstract. The variety of pathologies in burn diseases still poses a problem for extensive burns in the group of diseases with high mortality, and thus remains a therapeutic problem. The emergence of modern surgical dressings and instruments has changed the ways of thinking and acting in the surgical treatment of these enormous bodily injuries. Our actions in this respect bring tangible results in the form of reduced mortality and faster recovery. The work aims at comparing groups of patients treated before and after 2005. At the same time, modern technologies like silver dressings and the VersaJet knife were being implemented, the latter proving to be an essential tool in the surgical treatment of extensive body burns.
Keywords: excision of skin necrosis, free skin grafts, modern dressings, thermal burns

Streszczenie. Różnorodność patologii w chorobie oparzeniowej nadal stawia problem rozległych oparzeń w grupie chorób o dużej śmiertelności i stanowi ciągły problem terapeutyczny. Pojawienie się nowoczesnych opatrunków oraz narzędzi chirurgicznych zmieniło sposób postępowania i myślenia w leczeniu chirurgicznym tych olbrzymich obrażeń ciała. Nasze działania przynoszą wymierne efekty w postaci zmniejszenia śmiertelności i szybszego powrotu do zdrowia. Praca ma na celu porównanie grup oparzonych leczonych przed i po 2005 r. W tym czasie wdrożono nowoczesne technologie w postaci opatrunków srebrowych i noża VersaJet, które do dzisiaj (poza postępowaniem przeciwwstrząsowym) stanowią jedne z podstawowych narzędzi w chirurgicznym leczeniu rozległych oparzeń ciała.
Słowa kluczowe: oparzenie termiczne, wycięcie martwicy skóry, nowoczesne opatrunki, wolne przeszczepy skóry

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Introduction

People have dealt with the problem of thermal burns since time immemorial. They may be caused by random accidents, fighting or military combat. The first reports on burn treatment methods are found in Egyptian documents from before 1500 BC, which recommended applying honey and soil to the wounds. In ancient Greece, an oak bark infusion or a mixture of resin and pitch were used. Cooling the burn wound is already described in writings from the 9th century [1], whereas attempts to remove necrotic burn tissue surgically date back to the 17th century.

Currently, it has been established that burn eschar is the primary factor in the development of infection and all its general systemic consequences. It is a reservoir of bacteria that proliferate. The idea behind the early excision of the necrotic area is to remove the tissue that causes generalised infection and exhaustion of the organism.

A clean wound can be closed using skin grafts. Skin grafts were used to cover granulating wounds as early as in the times of Reverdin. In 1869, he described a method of collecting split-thickness skin flaps for grafting. The method was later promoted by Davis (1914), Humby (1936), and Padget and Hood (1946). The latter

popularised dermatomes, instruments for skin graft collection, still used in wound treatment today. In 1891, Lustgarten proposed excision of the burn necrotic tissue with immediate wound closure, and the first successful procedure was conducted by Williams in 1901 [2]. The instruments for excision of the necrotic tissue were constructed by Humby and Watson in the early 20th century [3]. The first procedures of burn wound excision and immediate graft distribution were performed by Janzekovic in 1961. Janzekovic proposed excision of 2nd degree burns to the level of the fascia using a surgical knife [4]. She popularised the method of tangential excision of necrotic tissue, providing good cosmetic and functional effects, as well as reducing blood loss. Bleeding from the burn wound is presently the primary factor limiting the scope of the surgery. In 1981, Janusz Domaniecki began studies on the reduction of bleeding from the surgical wound by using a CO_2 laser in procedures on parenchymal organs and soft tissues, including burn wounds [5].

The term “burn” has become a synonym of numerous pathological conditions. The multiplicity of general systemic disorders and complexity of pathologies associated with burn wounds elude clear definition and the constraints of one disease unit.

For instance, if a patient with chronic renal failure suffers an apparently harmless burn, it may exacerbate the kidney insufficiency, resulting in a direct life threat.

Minor burns usually do not pose therapeutic problems. However, a patient with a compromised immune system may develop a secondary infection in a small burn wound. In these cases, life-threatening complications, such as sepsis, may occur. Extensive burns in young people have a different prognosis than similar injuries in elderly patients. In elderly patients the prognosis is usually worse than in younger people with comparable burns. The assessment of the risk of death is the primary criterion when admitting patients to hospital; however, an individual approach is always required. The physician decides if a patient should be admitted, taking into consideration not only the prognostic scales, but also other factors, e.g. the affected site. The criteria for hospitalisation include burns to the face, hands, crotch, or injuries affecting such an extensive body surface area that, according to the physician, they may pose a threat to the patient’s life. Currently, the treatment of extensive burns usually involves interdisciplinary therapy, where constant co-operation between a surgeon and anaesthesiologist is supported by other specialists, depending on the changing condition of the patient. After treatment for severe burns, rehabilitation specialists join the team to assist the patient in regaining functional fitness. Recently, rehabilitation has been introduced in increasingly early stages of treatment, often when a patient is still receiving mechanical ventilation. According to specialists, it improves the outcomes and accelerates recovery. The medical team also includes psychiatrists and psychologists, as modern burn treatment consists not only in life saving, but restoring the ability to function in society. This usually applies to patients with burns to the exposed parts of the body. It is unacceptable to allow them to be pushed to the margin of social life due to post-burn deformities. This can sometimes lead to nervous breakdowns with tragic outcomes. Reconstructive surgery is of assistance in these cases. It involves various corrective or aesthetic procedures to eliminate the consequences of the burns. The first stage comprises procedures that help to restore proper function, usually releasing scar contractures. Frequently aesthetic medicine procedures are required to correct scars and improve the quality of the deformed skin. Until 2004, surgical management consisted in initial conservative treatment with the use of necrolytic ointments, until separation of the eschar. Then, assisted demarcation and free skin grafts on the prepared granulation tissue were applied. Burn wound excision by Humby knife and electric dermatome was then performed at a later stage than presently. The introduction of novel techniques involving the use of a VersaJet knife, negative pressure therapy and advanced skin replacement dressings resulted in the development and establishment of new standards in the surgical management of burns.

Aim of the study

The aim of the study was to compare the treatment outcomes between the burn patients treated at the Clinical Department of Plastic Surgery, Reconstruction Surgery and Burn Treatment, of the Military Institute of Medicine during two periods. The first period included patients receiving a traditional treatment in the years 1992-2004; the second comprised patients hospitalised in the years 2005-2010 and treated with advanced techniques (modern dressings, early excision of necrotic tissue using VersaJet).

Material and methods

Based on the medical records of burn patients receiving treatment on the ward, the medical history of 218 patients treated for burns in that period was analysed. The first group (Group 1) consisted of 126 patients (51.8%) receiving a traditional treatment method, and the second group (Group 2) involved 92 patients (42.2%) receiving the latest method.

In Group 1, apart from the anti-shock and general treatments dependent on the condition of the patient, which were similar in both groups, the first stage of therapy involved conservative treatment with necrolytic ointments, until separation of the burn eschar occurred. Next, assisted demarcation and free skin grafts on the prepared granulation tissue were applied. Excision of the burn wounds (burn necrotic tissue) by Humby knife and electric dermatome was performed later than in Group 2.

In Group 2, due to the VersaJet system, negative pressure therapy and skin substitute dressings available on the ward, the management reflected the present knowledge and technological advancement.

It followed the thesis that excision of the burn necrotic tissue is the principal condition for a gradual improvement of a patient's general condition, and prevents the development of multi-organ failure. Frequently, due to the patient's severe condition, the surface of a single excision of the necrotic tissue is reduced by up to a few per cent. A regular reduction of the burn surface area is important. Initially, free grafts of split-thickness skin are applied on the wounds simultaneously. When the amount of healthy skin for grafts is insufficient, modern skin substitute dressings are used. The wound after excision of the necrotic tissue is covered with dressings which help to preserve it in a condition suitable for future grafting, until the donor sites heal after initial harvesting. Then the skin is collected from the same donor sites. VersaJet technology allows one to debride burn wounds selectively, saving the healthy part of the dermis. It enables one to modify intraoperatively the assessment of the depth of the burn from 3rd degree to 2B. Leaving the wound under a modern dressing often results in spontaneous epithelialisation. The harvested skin may then be used on a different wound. Management is individualised for every patient. This therapy was not possible before the emergence of modern dressings and VersaJet technology.

In both groups the following parameters were analysed: number of patients, their sex, mean age, length of hospitalisation, number and percentage of deaths. The key management modification is the attempt to apply necrectomy early and frequently. Intensive therapy is conducted between the procedures to enable effective preparation of the patient for the next surgical procedure.

Results of the study

The results of the study are presented in the tables.

Table 1 shows the number and percentage of burn patients treated on the ward in the analysed periods. The first period was almost twice as long as the second one, but the mean number of burn patients treated per year was significantly higher in the second period (9.7 vs 15.3).

Table 2 shows the mean age of patients in both groups. In Group 1, the age of patients ranged from 11 to 82 years old, with a mean of 44 years. In Group 2, the age of patients ranged from 19 to 90 years old, with a mean of 49.3 years.

Table 3 shows the sex of patients in both groups. Group 1 comprised 40 female (31.7%) and 86 (68.3%) male patients. Group 2 comprised 25 female (27.2%) and 67 (72.8%) male patients.

Table 4 shows the number of surgeries, according to the severity of the burns. In patients with superficial burns, a single wound debridement was necessary. Deep burns required repeated procedures.

Table 5 shows the mean length of hospitalisation and the mean number of surgeries on the patients in both groups. In Group 1, the mean time of hospital stay was 40.6 days, which was 3.3 days longer than in Group 2. Similarly, the mean time from the admission of a patient to the hospital to the first surgery in Group 1 was 13 days, which was 2.2 days longer than in Group 2. The mean number of procedures was similar in both groups: 1.73 in Group 1, and 1.64 in Group 2.

Table 6 presents the data regarding the number and percentage of deaths in the analysed groups. In Group 1, 13 deaths were reported out of 126 patients (10.3%), and in Group 2, 4 patients out of the 92 died (4.3%).

Discussion

The term "traditional treatment" refers to a conservative therapy with the use of antibacterial and necrolytic ointments until the assisted demarcation of the necrotic tissue. "Surgical treatment" involves free split-thickness skin grafts on the debrided granulation tissue, sometimes following tangential necrectomy with the use of a dermatome and Humby knife. The term "advanced methods" refers to the use of VersaJet system, VAC, and silver skin substitute dressings.

Table 1. Group characteristics
Tabela 1. Charakterystyka grup

	Group 1	Group 2	Total
Number of patients	126	92	218
	57.8%	42.2%	100%

Source: Own data.

Table 2. Age-based characteristics
Tabela 2. Charakterystyka ze względu na wiek

	Group 1 (years)	Group 2 (years)
Mean patient age	44.0	49.3
Maximum patient age	82	90
Minimum patient age	11	19

Source: Own data.

Table 3. Sex-based characteristics
Tabela 3. Charakterystyka ze względu na płeć

	Group 1		Group 2		Total	
Female	40	31.7%	25	27.2%	65	29.8%
Male	86	68.3%	67	72.8%	153	70.2%
Total	126	100%	92	100%	218	100%

Source: Own data.

Table 4. Number of operations carried out depending on severity of patient's burn
Tabela 4. Liczba przeprowadzonych operacji w zależności od stopnia oparzenia pacjenta

	1st and 2nd degree burn patients	3rd and 4th degree burn patients	Total
	21	197	218
1 procedure	20	118	138
2 procedures	1	41	42
3 procedures	0	20	20
4 or more procedures	0	18	18

Source: Own data.

The analysis indicates that the present management results in a shorter recovery time and reduced mortality due to multi-organ failure. Procedures with the use of a hydro dissector reduces the time to recovery, as demonstrated by our observations. Another observation is the need for constant and regular reduction of the burn surface area, even with minor necrectomies involving a few per cent of the total body surface area, but conducted early and frequently, with primary wound closure. This results in a systematic improvement in a patient's general condition. Experience from the burn unit indicates that accurate assessment of the concurrent injuries is very important, as they affect considerably the course of treatment and mortality rates.

Table 5. Hospitalization duration - based characteristics
Tabela 5. Charakterystyka ze względu na czas hospitalizacji

	Group 1	Group 2
Mean number of days of hospitalisation	40.6	37.1
Mean time to operation	13.0	10.8
Mean number of operations	1.73	1.64

Source: Own data.

Table 6. Mortality
Tabela 6. Śmiertelność

	Group 1		Group 2	
Number of patients	126		92	
Number of deaths	13	10.3%	4	4.3%

Source: Own data.

Implementation of proper management already at the accident site is of key importance, and it includes cooling down the wound, securing the sufficient vascular access points, treatment of airways and introduction of fluid therapy, as well as a fast transfer of the patient to the burn unit. The experience in clinical practice dictates that the problem of burn treatment is not limited to the therapy of burn wounds alone. The role of modern combustiology is to enable patients to achieve normal functioning in society. In this context, the effectiveness of burn therapy as a comprehensive treatment was examined. The basic quantitative and qualitative analysis of the data presented in the tables justifies detailed conclusions.

The assessment of the burn degree in patients in Group 2 is unfavourable, compared to Group 1. A total of 94.6% of patients in Group 2 had 3rd degree burns, compared to 87.3% in Group 1. The x^2 test analysis did not reveal a statistically significant relationship between the degree of burns and the study group.

However, it should be emphasised that the effect of individual factors on the medical consequences of a burn is difficult to determine, as it is often impossible to assess the scope of a burn already at the hospital admission stage. Therefore, after the analysis of the data in patient records we decided to present the degree of burns only for information purposes. Such an approach results from insufficient data in some patients' records, as well as potentially significant differences in the assessment performed by different physicians.

Conclusions

Currently used surgical techniques can shorten the treatment of burn wounds.

An early first operation reduces the treatment time.

Advanced surgical therapy contributes to the increased survival of burn patients.

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Safety and efficacy of concomitant supraciliary microstenting with cataract surgery for treating open-angle glaucoma: 3-year experience

Skuteczność i bezpieczeństwo operacji usunięcia zaćmy z jednoczesnym wszczepieniem nadnaczyniówkowego implantu przeciwjaskrowego - obserwacje 3-letnie

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Abstract. This study evaluated the treatment outcomes of supraciliary microstent implantation (CyPass® Micro-Stent, Transcend Medical, USA) in patients with open-angle glaucoma undergoing cataract surgery. Prospective case series formed the material. Twenty patients (mean age: 76.5 ±7.1 years) were evaluated for 36 months following supraciliary microstent implantation combined with cataract surgery. Evaluated outcomes included IOP, best-corrected visual acuity (BCVA), number of required IOP-lowering medications, and adverse events. Baseline mean IOP (16.1 ±3.3 mm Hg) remained well-controlled at 36-months post-surgery (15.8 ±3.4 mm Hg; p =0.070). Baseline BCVA (mean 20/40 Snellen, range 20/25-20/200) was improved after surgery, and the effect was maintained for 36-months postoperative (mean 20/25 Snellen, range 20/20-20/80). All subjects used IOP-drugs at baseline (40% required >3 medications), whereas 80% remained medication-free at 36-months postoperative. One stent obstruction resulted in elevated IOP and device explantation. Another subject experienced persistent corneal oedema. Adverse events included transiently elevated IOP (20% of eyes) and hypotony (20%). Supraciliary microstenting combined with cataract surgery in open-angle glaucoma results in minimal complications and significantly reduced necessary IOP-lowering medications through the 36-month postoperative phase.
Key words: open-angle glaucoma, phacoemulsification cataract surgery, supraciliary microstent, supraciliary space

Streszczenie. Cel. Ocena wyników leczenia za pomocą mikroimplantu przeciwjaskrowego CyPass® u pacjentów z jaskrą otwartego kąta poddanych usunięciu zaćmy. Materiał. Badanie prospektywne typu case series. Metoda. 20 pacjentów (średnia wieku 76,5 ±7,1 roku) obserwowano przez 36 miesięcy po implantacji mikrostentu do przestrzeni nadnaczyniówkowej wykonanej z usunięciem zaćmy. Oceniano IOP, najlepszą skorygowaną ostrość wzroku *[best-corrected visual acuity* - BCVA), liczbę leków przeciwjaskrowych oraz powikłania. Wyniki. Przedoperacyjne IOP (średnia 16,1 ±3,3 mm Hg) regulowało się w 36-miesięcznym okresie obserwacji (15,8 ±3,4 mm Hg; p =0,070). Przedoperacyjna BCVA (średnia 20/40 wg Snellena, zakres 20/25-20/200) uległa poprawie i po 36 miesiącach wynosiła 20/25 wg Snellena (zakres 20/20-20/80). Wszyscy pacjenci przed zabiegiem stosowali krople przeciwjaskrowe (40% wymagało >3 leków), po 36 miesiącach 80% osób nie stosowało żadnych kropli. Jeden pacjent wymagał usunięcia implantu z powodu niedrożności z wysokim IOP Jeden pacjent miał przewlekły obrzęk rogówki. Inne powikłania to skok IOP (20%) i hipotonia (20%). Wnioski. Zastosowanie mikrostentu nadnaczyniówkowego w połączeniu z usunięciem zaćmy w jaskrze otwartego kąta daje istotną statystycznie redukcję IOP i stosowanych leków przeciwjaskrowych przy niewielkiej liczbie powikłań w 36-miesięcznym okresie obserwacji.
Słowa kluczowe: jaskra otwartego kąta, przestrzeń nadnaczyniówkowa, implant nadnaczyniówkowy, fakoemulsyfikacja zaćmy

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Introduction

Cataracts and glaucoma are the first and second leading causes of blindness worldwide [1]. Both conditions are age-dependent and frequently coexist [1, 2]. In the US, for example, nearly 26 million people were estimated to suffer from cataracts in 2014, and this prevalence is expected to increase to 30 million individuals by 2020 due to population ageing [2]. In 2014, approximately 2.9 million people in the US had glaucoma, and this number is projected to increase by over 20% to 3.4 million by 2020 [3]. Currently, 3.6 million Americans undergo cataract surgery annually, making it the most commonly performed surgical procedure in the US. Similarly, in the EU, 3.6 million cataract extractions were performed in 2014 [4], and this number will undoubtedly increase with ageing population demographics [5, 6]. Importantly, approximately 20% of patients receiving cataract surgery also present with a history of concurrent glaucoma [7]. Thus, a significant proportion of patients undergoing cataract surgery remain at risk of vision loss due to coexistent glaucoma. Open-angle glaucoma (OAG) is the most common glaucoma subtype, accounting for 74% of worldwide glaucoma cases [8], and an even larger proportion of US cases [4]. Elevated intraocular pressure (IOP) remains the sole modifiable risk factor for progressive optic neuropathy and vision loss in OAG [9]. Conservative medical therapies to reduce IOP in glaucoma frequently involve the simultaneous administration of multiple topical medications to reduce aqueous humor production or increase trabecular and uveoscleral outflow [9]. However, all of these drugs have potentially deleterious side effects [10] that require close follow-up, can be expensive [11], and often require life-long treatment regimens that can be confusing and inconvenient for patients, thereby compromising patient compliance and adherence to dosing schedules [12]. Numerous surgical approaches have been developed in efforts to overcome the need for often complicated and sometimes ineffective medication schedules intended to control ocular hypertension in OAG. Common interventions include laser trabeculoplasty and conventional trabeculectomy [9]. Laser treatment often provides good initial results, but their IOP-lowering effects are highly variable and frequently transient [13]. Conventional trabeculectomy is also an invasive procedure with significant potential side effects [9]. Thus, effective and minimally invasive glaucoma interventions are needed.

This need for effective and minimally invasive non-medical therapies for OAG has led to the introduction of *ab interno* microstent implant technologies that reduce IOP by bypassing areas of high outflow resistance thereby enhancing aqueous humor drainage via natural, physiological pathways [14, 15]. These approaches vary with respect to the mechanism of action, microstent design, implantation site, and surgical technique for device installation.

The CyPass® Micro-Stent (Transcend Medical, Inc., Menlo Park, CA, USA) is a novel ocular device that was designed to permanently normalize IOP in patients with OAG, by directing unimpeded aqueous humor outflow from the anterior chamber to the supraciliary space (SCS), a part of the uveoscleral outflow path. Targeting the uveoscleral pathway as a method of reducing IOP has some potential advantages. The IOP-lowering potential of the suprachoroidal space is well documented through the historical use of the iatrogenic cyclodialysis cleft [16]. Additionally, the prostaglandin analogues that are mainstays of glaucoma medical therapy largely function by enhancing outflow via the uveoscleral route [17].

This device has been approved for human use in the European Union since 2008, and in 2016 by the US Food and Drug Administration in an Investigational Device Exemption study, although recently it has been withdrawn due to endothelial cell loss after a 5 year period [18-20]. The current prospective case series evaluated the 36-month postoperative safety and efficacy profiles of the CyPass device after *ab interno* implantation into OAG patient eyes immediately following phacoemulsification and intraocular lens (IOL) implantation.

Materials and Methods

Study Design

This prospective, open-label, interventional, consecutive case series assessed OAG patient safety and outcomes after receiving a CyPass Micro-Stent implantation following phacoemulsification and IOL implantation. Surgeries were performed between January 2010 and December 2011 by one surgeon (M.R.).

Patients

Inclusion criteria were patients aged >18-years-old who required medication to control previously diagnosed primary or secondary OAG, and who had coexistent cataracts that were scheduled for phacoemulsification. One eye of each patient was included in the study; if both eyes qualified, the one with higher IOP values or with worse visual field parameters was selected. If both of these values were comparable, the eye with worse visual acuity was included in the study. The right eye was included in the study if the progression of glaucoma or cataract was comparable in both eyes. Exclusion criteria were prior surgery or laser trabeculoplasty in the eligible eye, clinically significant ocular pathology other than cataract and glaucoma, and diagnosis of acute angle-closure, narrow-angle, uveitic, neovascular, congenital, traumatic, or normotensive glaucoma in the study eye.

Preoperative Examination

The qualification process included taking the medical history concerning prior procedures and treatments. Comprehensive baseline eye examinations assessed the IOP (Goldmann tonometry), uncorrected distance visual acuity, best corrected visual acuity (BCVA), retinal cup/disc ratio, central corneal thickness, and axial length. Visual field tests and gonioscopic examination were also conducted.

Surgical Procedure

Anti-glaucoma medications were discontinued on the day of surgery. Topical medications for dilation and cycloplegia were used preoperatively. All surgeries were performed with retrobulbar anaesthesia (2% xylocaine, 0.5% bupivacaine, 150 IU hyaluronidase), and patients received bolus intravenous sedation/anxiolysis (50-100 µg fentanyl with 1-2 mg midazolam). Intraoperatively, blood pressure, O_2 saturation, and electrocardiography were monitored.

Phacoemulsification was performed through a 2.2 mm clear-corneal incision, and an AcrySof® IQ IOL (Alcon Laboratories Inc., Fort Worth, TX) was implanted. Irrigation was performed with a balanced salt solution containing 100 µg/ml vancomycin. The anterior chamber was filled with viscoelastic (Viscoat®, Alcon Laboratories), and intraocular acetylcholine chloride was administered to maintain pupil constriction and facilitate nasal angle visualization with a Swan-Jacob gonioscope (Ocular Instruments, Bellevue, WA) prior to and during microstent implantation. The implant was loaded onto the retractable guidewire of the applicator, inserted into the anterior chamber through the corneal incision, and advanced towards the scleral spur under gonioscopic guidance. The guidewire tip was used to bluntly dissect the ciliary body and create a passageway into the SCS. The microstent was then positioned within the newly created supraciliary duct, the guidewire was retracted, and the applicator was withdrawn from the eye. Viscoelastic was evacuated by saline irrigation and aspiration, and the integrity of the corneal incision closure was verified; no patient required corneal incision suturing. Microstents were implanted in the inferionasal quadrant. All patients were prescribed a steroid, NSAID, and antibiotic topical regimen for 1 month postoperatively.

Device Description

The CyPass® Micro-Stent (Transcend Medical, Inc., Menlo Park, CA) is constructed of flexible polyimide and is 6.35 mm long, with a largest external diameter of 0.51 mm and an internal diameter of 0.31 mm. The microstent has 76 µm-diameter fenestrations along its distal length to facilitate aqueous humor flux, and possesses three protruding retention rings at the proximal end for device stabilization within the SCS. The CyPass device is a supraciliary tube designed to permanently enhance aqueous humor outflow from the anterior chamber to the SCS. The device is provided by the manufacturer mounted on a curved introducer guidewire with a blunt dissection tip to facilitate insertion along the scleral curvature. When the guidewire is retracted after gonioscopy-guided device positioning within the angle and SCS, the CyPass device's natural elasticity causes slight rebound straightening that further anchors the microstent to the surrounding tissues. The device has received the Conformite Europeenne mark and is available for clinical use in Europe. The CyPass Micro-Stent is also the focus of an ongoing multicentre, randomized, controlled trial that is registered in the USA [20].

Postoperative Protocol

Follow-up ophthalmological examinations were performed on postoperative days 1 and 7, and months 1, 3, 6, 12, 18, 24, and 36. Eye examinations determined IOP, CDVA, and visual field, and the anterior and posterior segments were evaluated. Post-operative analyses included the occurrence of complications and the number of applied anti-glaucoma medications needed to maintain the target IOP *(i.e.,* <21 mm Hg). Safety-related outcome measures included intra-operative and postoperative adverse events (AEs). Effectiveness outcomes assessed during follow-up included changes from baseline IOP, BCVA, and number of glaucoma medications required to maintain target IOP in the operated eye.

Statistical Analyses

Descriptive statistics and paired two-tailed Student's t-tests were used to evaluate the data, which are provided as numbers and percentages of the patient population, and means ± standard deviation (SD) or 95% confidence intervals (95% CIs), with p-values <0.05 considered indicative of statistically significant differences between comparator groups. Statistical analyses were performed using Excel 2010 (Microsoft Corp., Redmond, WA) and Prism® v.5.03 statistical and graphing software (GraphPad Software, Inc., San Diego, CA).

Results

Patient demographics

This study included 20 eyes of 20 patients with OAG; 17 were primary OAG and 3 were secondary OAG. Group demographic data are given in Table 1. The cohort consisted of 19 females (95%) and 1 male (5%), with a mean age of 76.5±7.1 years at enrolment. Some patients missed follow-up visits for personal reasons unrelated to the study, so that N-values at postoperative 1, 2, and 3

year time points numbered 18 (90%), 16 (80%), and 15 (75%) eyes.

Intraocular pressure control and visual acuity

Mean preoperative medicated IOP was 16.1 ±3.3 mm Hg. Following surgery, IOP was significantly decreased by approximately 13% and 12% at the respective 6 and 12 month follow-ups (p =0.0082, and 0.0425; paired t-tests) (Figure 1A-B). At years 2 and 3 postoperative, respective IOP values were decreased *vs* baseline values by 9% (15.1 ±1.9 mm Hg) and 2% (15.8 ±3.4 mm Hg), though these differences were no longer statistically distinct (Figure 1B). Preoperative BCVA averaged 0.48±0.23 Units (≈20/40 Snellen) on the decimal scale (range 0.06-0.90 Units). After cataract replacement with an IOL and microstent implantation, BCVA significantly improved in a progressive fashion. The percentage of subjects with 20/25 or better BCVA was markedly increased from 10% of the cohort at baseline 72%, 81%, and 80% of the study subjects at years 1, 2 and 3 postoperative, respectively (p <0.001 at all time points by Fisher's exact test) (Figure 1C). Acuity increased immediately in 90% of patients by 1 week postoperatively (not shown). In 90% of the cohort, BCVA had significantly increased at 1 month postoperative versus the preoperative values, and this acuity either stabilized or continued to improve through the 36-month follow-up. Of the two patients whose BCVA had decreased at the 1-month examination, one patient displayed a negligible decrease from 0.6 to 0.5 units (from 20/32 to 20/40 Snellen), which improved to 0.8 units (20/25 Snellen) by 6 months. The second exception presented with a preoperative BCVA of 0.6 units, which fluctuated postoperatively to a low of 0.2 units (20/100 Snellen) at 36 months and returned to 0.4 units (20/50 Snellen) at 12 months. However, this patient's decreased acuity appeared in concert with early-onset corneal oedema (Day 1) and later-onset macular oedema (Month 3). Acuity continued to improve, and stabilized at 0.50 units through the 2- and 3-year time points.

Table 1. Patient demographics and baseline clinical parameters
Tabela 1. Wyjściowe dane demograficzne i kliniczne

N=20 eyes, from 20 patients	
age, years, mean ±SD	**76.5 ±7.1**
female, n (%)	19 (95%)
male, n (%)	1 (5%)
glaucoma type, n (%)	**20 (100%)**
primary OAG	17 (85%)
secondary OAG	3 (15%)
baseline IOP, mm Hg, mean ±SD	**16.1 ±3.3**
>21 mm Hg, n (%)	2 (10%)
<21 mm Hg, n (%)	18 (90%)
range	11-22 mm Hg
glaucoma medications, n, mean ±SD	**2.3 ±0.9**
3+ meds, n (%)	8 (40%)
2 meds, n (%)	8 (40%)
1 med, n (%)	4 (20%)
0 meds, n (%)	0 (0%)
prior glaucoma surgery/laser, n (%)	**0 (0%)**

Medications

Significantly fewer anti-glaucoma medications were used after surgery than before, throughout the entire 3-year follow-up (Figure 2). Mean preoperative anti-glaucoma drug use was 2.3 ±0.9 medications. At the 12-month follow-up, this number had been significantly reduced to 0.2 ±0.4 drugs (p<0.0001 *vs* baseline; paired t-test) (Figure 2A). At 2 and 3 years after intervention, mean glaucoma medication use remained significantly reduced at 0.4 ±0.5 and 0.5 ±0.6 drugs, respectively (p <0.0001 at both time points). No subject was anti-glaucoma drug-free at study entry. However, at 1, 2, and 3 years after microstent implantation, 83%, 81%, and 80% of the cohort did not require any glaucoma medications (p <0.0001 *vs* baseline for all follow-up points) (Figure 2B). At 1 year postoperatively, only 1 anti-hypertensive medication was required in the 17% of subjects that resumed drug use. At 2 and 3 years postoperative, of the ≈20% of subjects that required supplemental medication, none required more than 2 drugs.

At baseline, every study subject was using glaucoma medication to control IOP. After surgery, over 80% of the cohort was able to maintain IOP <21 mm Hg without medication through 3 years, and 67% realized a drug-free IOP <18 mm Hg (Figure 2C). At postoperative 3 years, 47% of the study subjects presented IOP <15 mm Hg without medication. Whereas 75% of the baseline population had IOP within the clinically targeted 6-18 mm Hg range, all of these individuals required medication to do so (Figure 2D). At 2 years postoperative, 100% of the participants maintained IOP within this aspirational pressure range, although only 19% were using glaucoma drugs. This effect was maintained through the 3-year follow-up, when 80% of the subjects remained within the target IOP range without supplemental medication.

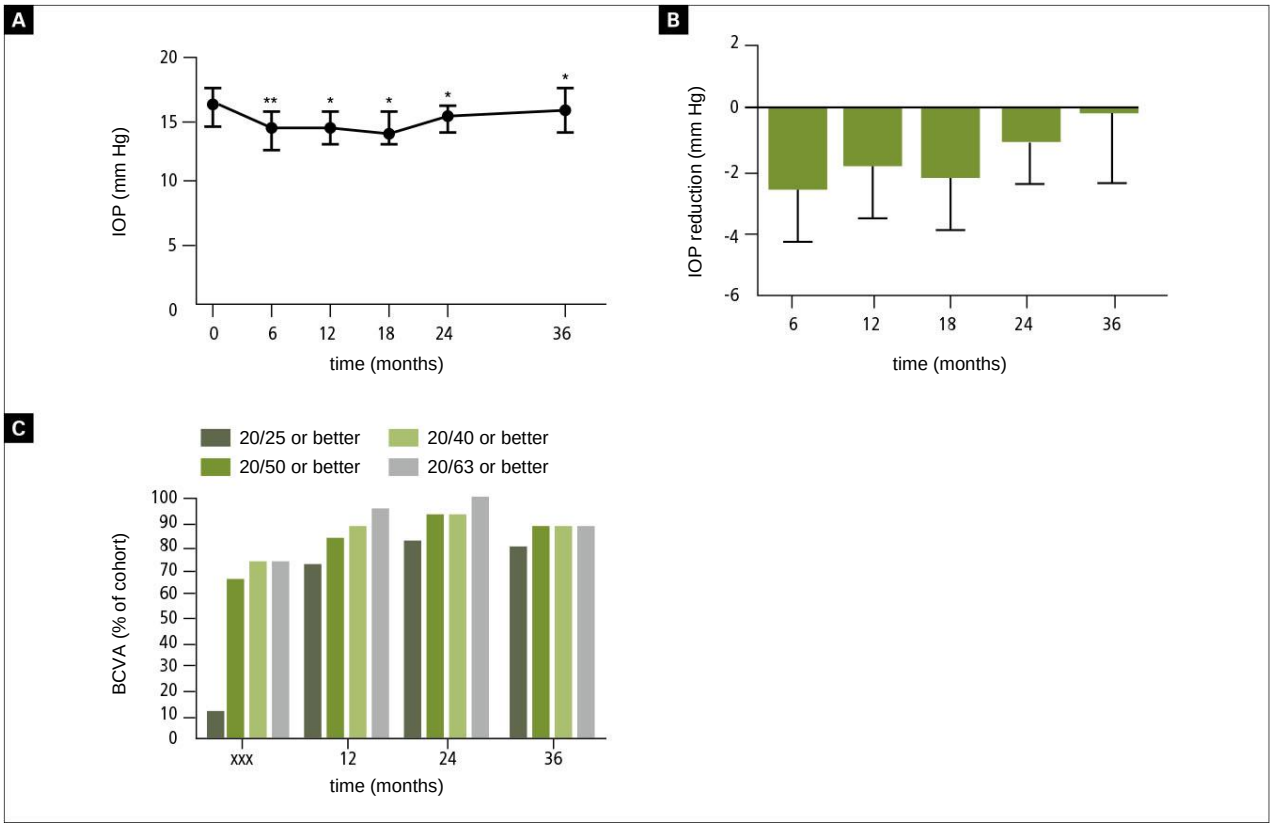

Figure 1. Intraocular pressure (IOP) and best corrected visual acuity (BCVA). A. Preoperative mean medicated IOP was 16.1 ±3.3 mm Hg (95% CI: 14.6—17.6 mm Hg). After CyPass Micro-Stent implantation with phacoemulsification cataract extraction, IOP significantly decreased by ≈12% by 18 months postoperative. At the 3-year study terminus, mean ±SD IOP was 15.8 ±3.4 mm Hg (95% CI: 13.9-17.7 mm Hg), which was not significantly different from baseline values (p >0.05 by paired two-tailed t-test). B. IOP was significantly reduced for 18 months following surgery, and did not exceed the baseline levels through 3 years postoperative. C. The percentage of subjects with 20/25 or better BCVA was markedly increased from 10% of the cohort at baseline 72%, 81%, and 80% of study subjects at 1, 2, and 3 years postoperative, respectively (p < 0.001 at all time points by Fisher's exact test). Values shown in Panels A and B are means with 95% confidence intervals (95% CIs).

Rycina 1. Ciśnienie wewnątrzgałkowe (IOP) i najlepsza skrygowana ostrość wzroku (BCVA). A. Przedoperacyjna średnia wartość IOP wynosiła 16,1 ±3,3 mm Hg (95% CI: 14,6-17,6). Po implantacji mikrostentu CyPass w połączeniu z fakoemulsyfikacją zaćmy IOP uległo znaczącej redukcji o około 12% w okresie 18-miesięcznej obserwacji. Po 3 latach średnia wartość IOP wynosiła 15,8 ±3,4 mm Hg (95% CI: 13,9-17,7) i nie była statystycznie różna od wartości przedoperacyjnych (p >0,05). B. IOP uległo znaczącej redukcji po 18 miesiącach od operacji i nie przekraczało przedoperacyjnych wartości wyjściowych w czasie 3 lat obserwacji. C. Odsetek przypadków grupy badanej z BCVA 20/25 lub lepszą wyraźnie się zwiększył z 10% przed operacją do 72%, 81% i 80% przypadków odpowiednio w 1., 2. oraz 3. roku obserwacji (p <0,001). Wartości pokazane na wykresach A oraz B są średnimi z 95% przedziałami ufności (95% CI).

Complications

Clinically significant adverse events (AEs) occurred in two patients (10%) during follow-up (Table 2). In the first case, stent obstruction with blood in the angle was noted at 2 weeks following surgery, with associated elevated IOP. A non-penetrating deep sclerectomy was performed in this subject with concurrent explantation of the microstent at the time of surgery, with no additional sequelae. The second case consisted of persistent corneal oedema (>3 months duration) starting 1 day after surgery. This subject also had an episode of macular oedema 3 months postoperatively, which was medically managed and resolved within 2 weeks following onset. Other anticipated minor AEs included transient elevated IOP (defined as IOP >30 mm Hg inclusive and more than 10 mm Hg higher than baseline IOP) in 4 patients (20%), and transient hypotony (pressure <6 mm Hg), also in 4 patients (20%), all resolving within 1 month.

Table 2. Adverse events
Tabela 2. Powikłania

***N=20 eyes, from 20 patients**	**•(% of cohort)***
high IOP (>30 mm Hg & B/L +10 mm Hg)	4 (20%)
≤1 mo. (Transient)	4 (20%)
>1 mo. (Persistent)	0 (0%)
hypotony (<6 mm Hg)	4 (20%)
≤1 mo.	4 (20%)
>1 mo.	0 (0%)
hyphaemia	**1 (5%)**
≤1 mo.	1 (5%)
>1 mo.	0 (0%)
corneal oedema	**1 (5%)**
≤1 mo.	0 (0%)
>1 mo.	1 (5%)
macular oedema	**1 (5%)**
≤1 mo.	1 (5%)
>1 mo.	0 (0%)
BCVA loss >2 Snellen lines	**0 (0%)**
microstent parameter requiring intervention	**1 (5%)**
malpositioned	0 (0%)
migrated	0 (0%)
obstruction requiring explantation	1 (5%)
miscellaneous	**1 (5%)**
anterior chamber shallowing	0 (0%)
cataract	0 (0%)
endothelial touch	0 (0%)
glaucoma disease progression	0 (0%)
macular changes, other than oedema	0 (0%)
retinal disease progression	0 (0%)
secondary glaucoma surgery	1 (5%)

*One subject had two adverse events in the study eye (corneal oedema and macular oedema)
IOP - intraocular pressure, B/L - baseline, BCVA - best corrected visual acuity

Discussion

Managing ocular hypertension in OAG patients is critical in mitigating vision loss and blindness. Pharmacological treatment, when effective, frequently involves multiple topical medications that must be self-administered on complicated schedules [9], resulting in poor patient compliance [12]. These IOP-lowering drugs are also expensive [11], must be used for a lifetime, and are not without side effects [10]. Conventional surgical approaches for enhancing aqueous drainage to correct IOP in OAG, such as the gold standard trabeculectomy, are invasive procedures that have a high rate of adverse events including visual acuity instability and loss, typically require close follow-up, often require adjunctive pharmacological therapy, and are prone to failure requiring re-operation [9, 13-15]. The CyPass Micro-Stent is implanted in a minimally invasive *ab interno* procedure that aims to overcome standard OAG treatment shortcomings by exploiting the unconventional uveosceleral outflow pathway. This microstent device is approved for clinical use in Europe and is currently undergoing phase III clinical trials in the US [18, 19]. Our OAG cohort received microstent implantation concurrent with phacoemulsification cataract surgery. Baseline IOP was generally well-controlled and target IOP was maintained for at least 36 months postoperatively. Importantly microstented eyes maintained the clinically-targeted IOP range in lieu of the markedly decreased numbers of IOP medications required during follow-up. Cataract phacoemulsification surgery itself has been shown to lower IOP in primary OAG eyes, likely by forming a deeper anterior chamber, but this effect appears modest in magnitude. Indeed, a 2014 report of 157 OAG patients indicated that, although mean baseline IOP in patients that underwent phacoemulsification decreased during the 1-year follow-up, 38% of eyes with medication-controlled OAG had worsened IOP control after surgery, with 24% requiring additional drugs or laser trabeculoplasty [21]. Another long-term study indicated no significant difference in IOP medication use in OAG eyes 3 and 5 years after cataract surgery [22], whereas another group reported that phacoemulsification reduced hypotensive medication use in OAG patients by 0.4 ±0.9 medications at 24 months [23]. Thus, consensus remains to be established regarding variable IOP responses to cataract surgery in OAG patients. Garcia-Feijoo et al. show that CyPass Micro-Stent surgery without cataract removal effectively lowered IOP, precluding the need for more invasive glaucoma surgery in over 80% of patients at 1 year, thereby reducing postoperative glaucoma surgical complications. There were no serious intraoperative adverse events. The most common adverse events included IOP increases >30 mm Hg (11%), transient hyphaemia (6%), and cataract progression (12%). Mean IOP was reduced by 34.7%. Mean medication usage was also reduced from baseline 2.2 (±1.1) to a mean of 1.4 ±1.3 at 12 months [24]. The multicentre, prospective case series (136 eyes with OAG) showed that no sight-threatening adverse events occurred within the 24-month postoperative period after CyPass Micro-Stent implantation combined with phacoemulsification. The most common adverse events were transient (<1 month onset) hypotony (15.4%) and microstent obstruction (8.8%), typically due to iris tissue overgrowth.

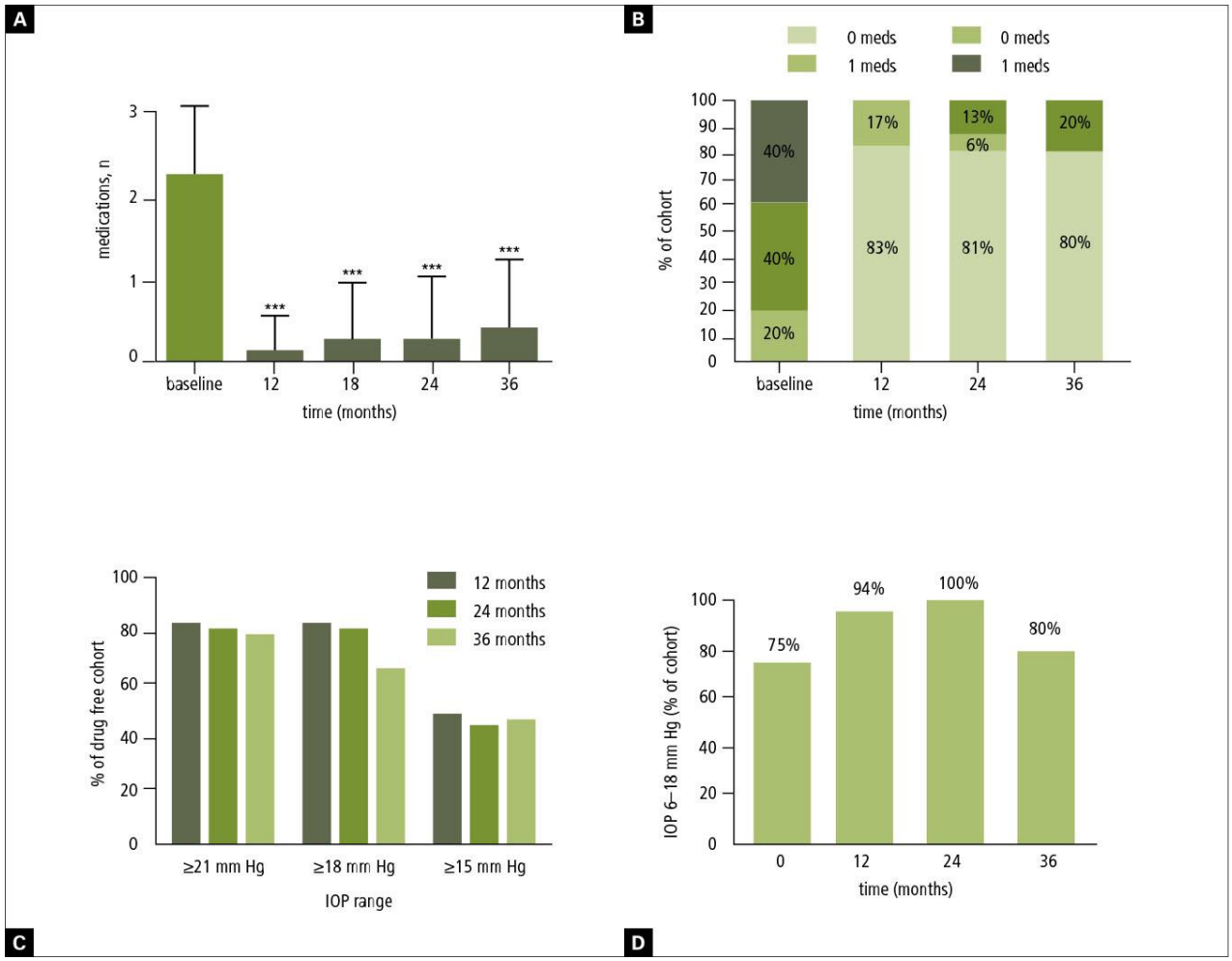

Figure 2. Topical anti-hypertensive glaucoma medication use. A. The average number of preoperative IOP-lowering medications used by this cohort was 2.3 ±0.9 drugs (95% CI: 1.9-2.6 drugs), and no patient was drug-free before cataract extraction and microstent implantation surgery. Glaucoma medications were dramatically reduced to 0.2 ±0.4 drugs (95% CI: 0.0-0.4 drugs) at 12 months, and maintained at 0.4 ±0.8 (95% CI: -0.1-0.9 drugs) through 36 months following surgical intervention with microstent implantation (***p<0.001 at both follow-up times *vs* baseline, unpaired t-test; shown are mean ±SD). B. Before surgery, no subject was IOP drug-free, and 40% were using >3 drugs. At the 12-month follow-up, a significantly increased 83% of patients were drug-free, and the remaining 17% were using only one IOP-reducing medication (p<0.001 by Fisher's exact test). At 3 years postoperative, 80% of the cohort remained medication-free. C. Through 3 years, surgical intervention resulted in similarly elevated proportions of subjects having stably improved IOP control in the operated eye while remaining medication-free. D. Microstenting with cataract surgery increased the proportion of subjects, with or without anti-glaucoma medication use, to maintain IOP in the 6-18 mm Hg range.

Rycina 2. Liczba stosowanych leków przeciwjaskrowych. A. Średnia liczba przedoperacyjnych leków obniżających IOP stosowanych w grupie badanej wynosiła 2,3 ±0,9 leku (95% CI: 1,9-2,6), nie było żadnego pacjenta bez miejscowej terapii przeciwjaskrowej przed operacją usunięcia zaćmy i implantacji mikrostentu. W ciągu 12 miesięcy liczba stosowanych leków przeciwjaskrowych uległa znacznej redukcji do 0,2 ±0,4 (95% CI: 0,0-0,4) i utrzymywała się na poziomie 0,4 ±0,8 (95% CI: -0,1-0,9) przez 36 miesięcy)*** p <0,001 w obu okresach obserwacji w stosunku do wartości wyjściowej, test t Studenta dla prób niezależnych, pokazano średnią ±SD). B. Przed operacją w badanej grupie nie było żadnego pacjenta bez miejscowej terapii przeciwjaskrowej, a aż 40% stosowało co najmniej 3 leki. W 12-miesięcznym okresie obserwacji istotnie zwiększył się odsetek pacjentów bez leków do 83%, a pozostałe 17% stosowało tylko jeden lek (p <0,001). W 3. roku obserwacji 80% badanej grupy pozostało bez leków. C. Przez 3 lata obserwacji przeprowadzona procedura chirurgiczna skutkowała zwiększeniem odsetka osób z dobrze kontrolowanym IOP w operowanym oku bez konieczności stosowania miejscowych leków przeciwjaskrowych. D. Implantacja mikrostentu w połączeniu z chirurgią zaćmy zwiększa odsetek pacjentów z lekami przeciwjaskrowymi lub bez leków z dobrze kontrolowanym IOP w zakresie 6-18 mm Hg.

A total of 4.4% of the eyes required secondary incisional glaucoma surgery. High IOP (>30 mm Hg and >baseline IOP + 10 mm Hg) occurred in 4.4%, and 11% of the eyes needed secondary glaucoma surgery. At 24 months, there was a sustained effect involving the reduction of both medication use and IOP reduction [25].

In the two-year COMPASS trial, 374 eyes had cataract surgery with cypass implantation, with unmedicated IOP decreased from 24 ±2.8 mm Hg before surgery to 17.0 ±3.4 mm Hg. The surgery significantly reduced hypotensive ocular medication usage from the baseline 1.4 ±0.9 to 0.2 ±0.6 after 24 months. A total of 84.8% of

the subjects were medicine free after 24 months which is similar to our results. 39% of the eyes had transient complications like visual acuity loss >2 Snellen lines, iritis, corneal oedema, hypotony, and cyclodialysis cleft. Nearly all were resolved by the end of the trial. Moreover, the complication rate was not significantly higher than in phacoemulsification alone group. The authors did not notice any vision-threating microstent-related adverse events [26]. The iStent (Glaukos Corp., Laguna Hills, CA) is a metal microstent that is implanted within the Schlemm's canal to enhance trabecular outflow [27]. The iStent main efficacy end-point in a 2012 report of results from concurrent microstenting with cataract surgery was the proportion of subjects with IOP <21 mm Hg without needing IOP medication [28]. At 2 years postoperative, this criterion was achieved by 61% of iStented subjects. Though our study did not employ washout IOP measurements, 100% of our cohort were medication-dependent at baseline, with 40% using >3 drugs. This was sustainably reduced to 17-20% of participants requiring drugs at 1-3 years postoperative. At the 2-year comparator point, 81% of our cohort were IOP medication-free, and all subjects maintained IOP within a more stringent 6-18 mm Hg range. The Hydrus appliance (Ivantis Inc., Irvine, CA) is another metal microstent that targets Schlemm's canal. A 2015 report on OAG subjects undergoing microstenting with cataract surgery indicated a medication-free rate of 73% at 2 years postoperative [29], similar to the 81% rate we currently report with the CyPass Micro-Stent. The Hydrus cohort required 2.0 mean medications at baseline, which decreased to 1.0 drugs in microstented subjects at 2 years; in the current CyPass study, mean medication use was reduced from 2.3 at baseline to 0.4 drugs at 2 years postoperative, a value that remained stable (0.5 medications) for the 3 years. In our trial, microstent implantation performed concurrently with phacoemulsification markedly and sustainably reduced the need for medications to control IOP in subjects with OAG. Here, 80% of participants maintained target IOP values while remaining entirely drug-free through the 3 years of follow-up, whereas all patients were anti-glaucoma drug-dependent before intervention. Visual acuity significantly improved after dual cataract extraction / micro-stent implantation, and this effect was observed as early as 1 month postoperative, with continued improvement and maintenance through the 3-year follow-up. Thus, we have no evidence that contraindicates installing the CyPass device during routine cataract surgery due to vision degradation. Future prospective studies comparing phacoemulsification alone to combined cataract surgery with microstent implantation should provide more definitive assessments of potential microstent treatment effects on visual acuity. No surgical procedure is entirely devoid of potential complications. Two patients experienced serious AEs in our cohort. One case of microstent obstruction associated with hyphaemia, elevated IOP (transient; maximum 45 mm Hg), and blood in the angle necessitated device explantation at 3 weeks postoperative. A prior iStent report indicated a similar 4.3% incidence of microstent obstruction through 24 months of follow-up [28]. In our study, another patient experienced a single transient (<2 weeks) instance of macular oedema that began at 3 months postoperative; this patient also displayed persistent corneal oedema with immediate postoperative onset that lasted 6 months. Though the aforementioned iStent RCT reported a cumulative 17.2% rate of diverse anticipated minor AEs for 24 months [28], their published results do not detail the specific incidence of corneal oedema alone. The Hydrus study reported a low AE rate; however they observed focal peripheral anterior synechiae in 19% of the microstented subjects [29], which did not occur in our cohort. Minor AEs in our study comprised transiently elevated IOP and hypotony. Limited patient numbers may have skewed our true AE rate; indeed, another recent clinical trial of 184 patients that underwent dual phacoemulsification/CyPass Micro-Stent implantation reported no serious AEs though 6 months follow-up [19].

Conclusions

Implanting of a supraciliary CyPass Micro-Stent concurrent with cataract surgery is a safe and minimally-invasive open-angle glaucoma treatment option that reduces necessary intraocular pressure-lowering medications through the 36 month postoperative period. Study limitations include a relatively small cohort size and a single-arm protocol that precluded assessing the potential impact of cataract surgery on stent-mediated OAG outcomes. The lack of a medication "wash-out" at baseline visit was a limitation too. Nonetheless, this efficacy and safety study is related to a much larger multicentre clinical trial still in progress [20], and provides important new information regarding the utility of concomitant microstent implantation during routine cataract surgery. The microinvasive nature of this procedure holds significant promise in effectively treating ocular hypertension in OAG, in this case using the same clear corneal incision created for cataract extraction. Given the unpredictable outcomes of more invasive OAG surgical interventions, and the already high yet still-increasing costs of IOP-lowering medications [11], the supraciliary CyPass device may prove to be an effective minimally-invasive glaucoma treatment option that reduces or precludes the need for pharmacological support.

Ethical approval

This study was conducted under the auspices of the Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients before the procedure.

Conflict of interests

Apart from receiving study funding from Transcend Medical, no author has any conflict of interest, financial or otherwise, to declare.

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Use of VAC® therapy in the treatment of massive injuries of the chest front wall. A case report

Wykorzystanie terapii podciśnieniowej VAC® w leczeniu rozległego urazu przedniej ściany klatki piersiowej. Opis przypadku

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Abstract. Multiple organ trauma are currently among the most frequent causes of death, and massive chest injuries have a very high mortality rate. The paper presents the model of interdisciplinary treatment of the patient who underwent a massive chest injury caused by an agricultural machine. The therapy involved the latest treatment methods, such as VAC® therapy, hydro surgery system - VersaJET and the specialist dressings. The patient was transported by the Air Rescue Service to the Military Institute of Medicine, where he initially underwent immediate clamshell thoracotomy to allow provisional control of the injury. Then, due to the symptoms of septic shock and the massive infection of the chest front wall soft tissues, VAC® therapy and the VersaJet system were introduced. The latter was used to remove necrosis and cleanse the infected tissues. Simultaneously, an intensive multidirectional treatment was performed in the Intensive Care Unit. This included broad-spectrum targeted antibiotic therapy and nutritional therapy. After the patient's condition was stabilized and the injured tissues condition improved, it was decided to perform reconstruction of the front wall of the chest with the musculocutaneous flap from the musculus lattissimus dorsi, which was used to close the large loss of tissues in the front wall of the chest.
Key words: chest injury, damage control surgery, negative pressure wound therapy, thoracotomy, VAC®, VersaJet

Streszczenie. Urazy wielonarządowe należą obecnie do najczęstszych przyczyn zgonów na świecie, a otwarte urazy klatki piersiowej są obarczone bardzo dużą śmiertelnością. W pracy opisano model wielodyscyplinarnego leczenia pacjenta po masywnym urazie klatki piersiowej spowodowanym przez maszynę rolniczą. W terapii wykorzystano najnowocześniejsze metody leczenia, obejmujące terapię podciśnieniową VAC®, zastosowanie noża wodnego VersaJet oraz opatrunków specjalistycznych. Chory został przetransportowany do Wojskowego Instytutu Medycznego przez zespół Lotniczego Pogotowia Ratunkowego, gdzie pierwotnie poddany został zabiegowi torakotomii sposobem „clamshell" w trybie natychmiastowym, co umożliwiło pierwotne zaopatrzenie odniesionych obrażeń. Następnie ze względu na cechy wstrząsu septycznego i masywne zakażenie tkanek miękkich przedniej ściany klatki piersiowej wykorzystano do leczenia terapię podciśnieniową (VAC) oraz system VersaJet, którym usunięto martwicę i oczyszczono zakażone tkanki. Jednocześnie prowadzono intensywne leczenie wielokierunkowe na Oddziale Intensywnej Terapii, obejmujące szerokospektralną antybiotykoterapię celowaną i leczenie żywieniowe. Po ustabilizowaniu stanu chorego oraz uzyskaniu poprawy w obrębie tkanek objętych urazem zdecydowano o wykonaniu operacji rekonstrukcyjnej z użyciem uszypułowanego płata skórno-mięśniowego (wykorzystując mięsień najszerszy grzbietu), którym zamknięto rozległy ubytek przedniej ściany klatki piersiowej. **Słowa kluczowe:** uraz klatki piersiowej, torakotomia, terapia podciśnieniowa, VAC®, VersaJet, *damage control surgery*

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Introduction

In Poland, thoracic injuries are associated with a 25% mortality rate, and are observed in approximately 50% of multiple injury cases. Approximately 80% of isolated thoracic injuries are associated only with pain due to rib fracture, and contusion of the chest muscles and soft tissues [1]. The remaining 20% of cases are life-threatening, due to respiratory failure (15%) and hypovolemic shock (5%). Every case of open chest injury is an indication for urgent thoracotomy. Moreover, thoracic injuries, depending on the direction and force of trauma, may be associated with mediastinal damage. In 20% of cases, trauma to multiple adjacent organs is observed at the same time: 70% of them are lung injuries, and 20% are oesophageal injuries [3]. Specialist treatment of the above injuries should be conducted in multispecialty facilities, by interdisciplinary teams, and using the most advanced therapeutic methods. Negative-pressure therapy is commonly used in wound treatment; however, in recent years its role in trauma surgery has been increasing [2]. Negative-pressure dressings are used with success as an excellent method of temporary closure of the abdominal cavity [2]. The concept of "damage control surgery" comprises three stages in patient management: surgical procedure and control of the primary source of bleeding, followed by control of the sequelae of the shock at the Intensive Therapy Unit, and final treatment of the injury, involving secondary wound closure during the last stage of the therapy. The management presented below was based on the premises of damage control surgery, and the use of advanced treatment methods, such as VAC®, VersaJet, special dressings, broad spectrum antibiotics and medical nutrition ensured a comprehensive treatment of the injury, and adequate preparation of the patient for reconstructive therapy.

Case report

A 46-year-old patient (P.S., 2015-83192) was transported by the Medical Air Rescue to the Military Institute of Medicine due to massive thoracic injury caused by an agricultural machine (fertiliser spreader). The trauma resulted directly from contact with a rotating element of the machine. On admission to the ED the patient was lucid. He was intubated and received a bilateral clamshell thoracotomy (transverse thoracotomy).

Figure 1. Front wall of the chest with a massive inflammatory process
Rycina 1. Przednia ściana klatki piersiowej z masywnym procesem zapalnym

During the procedure, intensive haemorrhage from the right thoracic artery and intercostal arteries was observed (in the area of sternal body fracture), as well as intensive haemorrhage from the inferior lobe of the left lung, where an approximately 10 cm long tear was visible, and from the anterior mediastinal tissue. The bleeding was controlled. The right and left pleural cavities were rinsed with Microdacyn (superoxidised solution).

The patient was examined by a cardiac surgeon intraoperatively; a transoesophageal ECHO examination excluded tamponade or damage to the major vessels. Next, primary sternal stabilisation with metal sutures (loop) was performed, the wound cleaned and disinfected, then closed with situational sutures.

Immediately after the procedure the patient was transferred to the Intensive Therapy Unit, where intensive multidirectional treatment was introduced. The patient received pressor amines for cardiovascular support, mechanical ventilation was continued, and significant soaking of the dressings with serous exudate and blood was observed.

A physical examination revealed signs of subcutaneous emphysema in the area of the chest and abdominal wall. During further hospitalisation, the inflammatory markers in the laboratory tests were elevated, and the patient's body temperature was temporarily increased. Thoracic computed tomography demonstrated bilateral subcutaneous and intramuscular emphysema, as well as massive thickening of the pleura and suspected pleural abscesses. Turbid exudate was found locally, in the wound area. Based on the interpretation of the computed tomography test and the local status, the patient was qualified for negative-pressure therapy (Figure 1).

Figure 2. Negative pressure therapy applied
Rycina 2. Założony opatrunek podciśnieniowy

Figure 3. Use of VersaJet system
Rycina 3. Użycie systemu VersaJet

The patient received another surgical procedure, which revealed large quantities of malodorous fluid in the wound (cultures were collected), massive infection, and macroscopic signs of extensive inflammation, involving the pericardial sac. Necrectomy with the use of VersaJet water dissector was performed (Figure 2), and necrotic tissues were removed until the actively bleeding layer was exposed. Elements of the sternum and ribs were also cleaned. Both pleural cavities were redrained, the wound was rinsed and disinfected with hypochlorite solution (Microdacyn®). The deficit in the thoracic wall over the pericardial sac was dressed with Adaptic, isolating the pericardial sac from the negative-pressure dressing. Individual sutures were applied on fragments of the sternum and the intercostal area. A WhiteFoam negative-pressure dressing was placed inside the wound, then GranuFoam was applied, and therapy was initiated. Initially, negative pressure of -50 mm Hg was used, then gradually increased to -100 mm; no changes in the ECG record or in the ventilation parameters were found.

After three days the dressing was changed. A significant improvement in the local condition and reduction of macroscopic signs of inflammation was observed intraoperatively. Purulent content was aspirated from the right and left pleural cavity. Considering the above, negative-pressure therapy was applied directly in the right and left pleural cavity. Following the removal of a limited amount of necrotic tissue from the wound, an Adaptic dressing was sewn over the non-adhesive WhiteFoam dressing, and introduced into the right and left pleural cavity, covering the palpably accessible lung fragments. The pericardial sac was dressed similarly, and everything was joined using the bridge dressing technique. Therapy with the use of gradually increasing negative pressure of -50/-75/-100/-125 mm Hg was continued. No abnormalities in the patient's vital parameters or ECG records were observed during this procedure.

After two days a re-operation was performed. Further improvement was found intraoperatively, but due to the presence of small quantities of necrotic tissue in the inferior pole of the wound, it was debrided again with a water dissector. Revision of the pleural cavities revealed no signs of pleural abscess. The wound was disinfected with hypochlorite and partially closed. Non-adhesive WhiteFoam dressings were re-applied to both pleural cavities, following the same pattern. A tracheostomy was performed at the same time. During the following change of VAC dressing (Figure 3), further improvement in the wound was observed, and laboratory tests demonstrated reduced inflammatory markers. A plastic surgeon was requested to give an intraoperative consultation, and he qualified the patient for reconstructive surgery. Until then, negative-pressure therapy was continued (2 changes of dressings), drains were removed from the right and left pleural cavity, and the bone elements were developing granulation tissue, bleeding on contact.

The local condition and improved general status of the patient allowed reconstructive surgery to be performed, during which an insular flap was prepared in the latissimus dorsi muscle, with a vascular pedicle up to the axillary fossa. Tunnelisation of the lateral thoracic wall

Figure 4. Patient after reconstructive procedures
Rycina 4. Pacjent po zabiegu rekonstrukcyjnym

was performed, to ensure communication with the post-trauma deficit. The pediculated flap was moved through the prepared tunnel, with the deficclosed in the anterior thoracic wall (Figure 4).

The tissue deficit after the flap preparation was covered with a split-thickness skin graft collected from the left thigh. In the post-operative period a significant improvement was observed in the patient's general status, and the wound healed normally, with a limited support of negative-pressure therapy. The patient was discharged after 9 weeks of hospitalisation, in a good general and local condition.

Discussion

Treatment of patients with multiple injuries requires a comprehensive, multispecialty background, and intensive interdisciplinary management. The use of VAC therapy and water dissector provided prompt control of the local infection, and the signs of inflammation in the trauma wound. During the negative-pressure therapy in the described case the greatest difficulty was associated with the location of the negative-pressure dressings directly on the lung parenchyma and in the pericardial sac, which could result in impaired respiratory mechanism or disturbed cardiac rhythm. These problems were not encountered during the treatment, and adverse effects were minimised by gradually increasing the negative pressure values, and careful monitoring of the patient's status. The use of Adaptic dressings allowed separation of the pericardial sac from the non-adhesive negative-pressure dressing, while preserving the function of the negative-pressure therapy. Apart from the surgical treatment, the supportive therapy including broad-spectrum antibiotics based on the cultures grown, while enteral and parenteral nutrition played an important role, helping to stabilise the patient's condition.

Conclusion

The scope of the negative-pressure therapy, as demonstrated in this study, currently includes the mediastinum and "open" thorax. This treatment method is now established and its valued in the emergency surgical procedures as well. The use of the discussed method in the treatment of mediastinal infections has significantly reduced the mortality rates and improved treatment outcomes in infections following cardiac surgeries [4].

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Difficulties in the diagnosis of organizing pneumonia in primary care. A case report

Trudności w diagnostyce organizującego się zapalenia płuc w praktyce lekarza rodzinnego. Opis przypadku

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Abstract. Organizing pneumonia is a rare interstitial lung disease. It may be cryptogenic or secondary. A case of organizing pneumonia, probably secondary to *Pneumocystis jiroveci* infection, is described. A 57-year-old man with cough, weakness and fever consulted a general practitioner. A chest radiography was performed, which suggested malignant disease. However, a chest computed tomographic scan suggested organizing pneumonia. The patient was referred to a respiratory diseases hospital, where the diagnosis was confirmed. Moreover, genetic material *of Pneumocystis jiroveci* was found in PCR from a bronchoalveolar lavage. Glucocorticoids, trimethoprim/sulfamethoxazole and bronchodilators were introduced. Due to the treatment the patient's condition improved, but the adverse effects of corticosteroid therapy occurred, which required the special attention of general practitioner.

Keywords: adverse effects of glucocorticoids, interstitial lung diseases, lung function tests, organizing pneumonia, *Pneumocystis jiroveci*

Streszczenie. Organizujące się zapalenie płuc należy do grupy rzadkich chorób śródmiąższowych płuc. Wyróżnia się przypadki o nieznanej etiologii oraz postacie wtórne. Przedstawiono przypadek organizującego się zapalenia płuc, najprawdopodobniej wtórnego do zakażenia *Pneumocystis jiroveci.* Choroba rozwinęła się u 57-letniego mężczyzny, który zgłosił się do lekarza rodzinnego z powodu kaszlu, osłabienia i gorączki. Obraz radiologiczny klatki piersiowej wskazywał na proces nowotworowy, ale w tomografii komputerowej zmiany odpowiadały organizującemu się zapaleniu płuc. Chory został przyjęty do kliniki chorób płuc, w której potwierdzono rozpoznanie. W popłuczynach oskrzelowych pacjenta wykryto materiał genetyczny *Pneumocystis jiroveci.* Wdrożono leczenie glikokortykosteroidami, trimetoprimem z sulfametoksazolem oraz lekami rozszerzającymi oskrzela, po których stan chorego uległ poprawie, ale pojawiły się działania niepożądane steroidoterapii, wymagające starannej opieki przez lekarza podstawowej opieki zdrowotnej.

Słowa kluczowe: badania czynnościowe płuc, choroby śródmiąższowe płuc, organizujące się zapalenie płuc, *Pneumocystis jiroveci,* niepożądane działania glikokortykosteroidów

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Introduction

Organizing pneumonia (OP) is a disease classified as an interstitial pneumonia [1]. There have been cases of unknown aetiology (cryptogenic organizing pneumonia) and secondary forms, caused by infections or induced by drugs or radiation, as well as developing in the course of connective tissue disorders or following organ transplantation [2, 3]. In patients with OP the epithelium of the pulmonary alveoli and alveolar-capillary barrier is

damaged, with exudate formation. In the histopathological picture, a repair process in the lung parenchyma is visible, characterised by the presence of polypoid fibrosis filling the lumen of the small airways [2]. Organizing pneumonia is a rare disease with a poorly defined epidemiology [2]. The annual incidence in Iceland was 2/100 thousand [4]. The clinical picture of OP, laboratory and radiological test results indicate pneumonia, but antibiotic therapy is unsuccessful, and delays the proper diagnosis [2, 3]. High-resolution computed tomography typically reveals irregular, diffused, bilateral patchy parenchymal densities, together with "ground glass" opacities, with an air bronchogram [5]. Functional tests of the respiratory system usually demonstrate mild restrictive changes, and reduced gas diffusion capacity [5]. The diagnosis is based on the histopathological assessment of lung samples [2, 5]. Glucocorticosteroids are the treatment of choice [6]. The exact initial dose or duration of therapy have not been established. After dose reduction or withdrawal of therapy, recurrence of the disease is frequently observed [7]. Macrolides, cyclosporin and cyclophosphamide are also used in the treatment of OP [6]. Prognosis in this disease is very good, provided a suitable therapy is applied [2].

The case of OP presented below was probably caused by a *Pneumocystis jiroveci* infection. Glucocorticosteroids improved the condition of the lungs, and also induced the number of adverse reactions.

Case report

A 57-year-old male, physical worker, smoking (30 pack-years), reported to the primary care physician due to a febrile state, up to 38.3°C persisting for 2 weeks, weakness, productive cough and night sweats. Eight years before the patient was diagnosed with chronic obstructive pulmonary disease (COPD) by a primary care physician. The spirometry performed at that time demonstrated FEV_1/FVC 63%, FEV_1 69%. Ipratropium bromide and formoterol were prescribed, but the patient did not use them and did not attend the follow-up visits. During the first visit his condition was good. A physical examination revealed obesity (BMI 33 kg/m^2), RR 140/90 mm Hg, HR 100/min, SaO_2 98%, 14 breaths/min, and vesicular sound over the lung fields. The laboratory tests ordered by the primary care physician demonstrated increased erythrocyte count (6.23 x 10^6/ml), increased sedimentation rate (ESR 21 mm/h), elevated haematocrit (54.2%), and elevated concentrations of haemoglobin (17.9 g/dl), total cholesterol (222 mg/dl) and glucose (109 mg/dl).

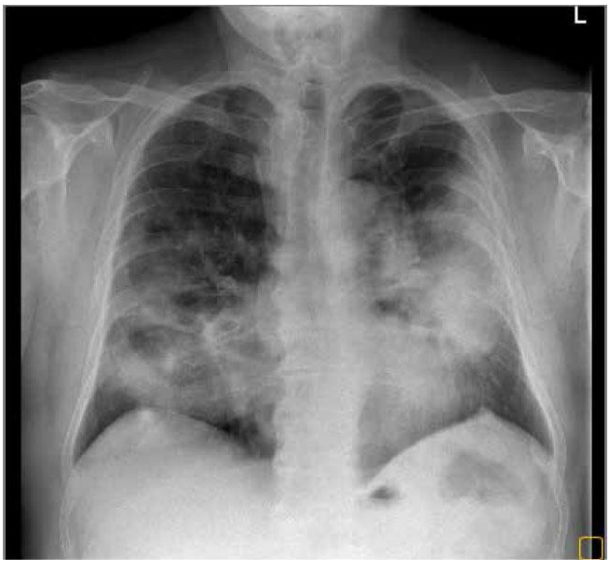

Figure 1. Postero-anterior chest X-ray. Massive consolidations in the middle and lower lungs, especially on the left.
Rycina 1. Zdjęcie radiologiczne klatki piersiowej w projekcji tylno-przedniej. Masywne plamiste zagęszczenia w polach środkowych i dolnych płuc, większe po stronie lewej.

A thoracic X-ray revealed diffused, round shadows in both lung fields, and dilated left hilum, suggesting a diffused neoplastic process (Figure 1). The patient was referred to an oncologist for an urgent consultation.

The computed tomography examination of the thorax, performed in the oncological centre, demonstrated massive alveolar consolidations, located mainly in the lower and middle lungs, in the form of peribronchiolar merging large nodular lesions, with air bronchogram, with band-like shadows around the infiltrations; some of the lesions were surrounded by "ground-glass" opacities (Figure 2). The picture suggested organizing pneumonia, differentiated with lymphoma, Kaposi's sarcoma and lepidic predominant adenocarcinoma. The oncologist introduced empirical antibiotic therapy (amoxicillin and clavulanic acid), and referred the patient for a consultation with a pulmonologist. As a result, the patient was admitted to the Department of Lung Diseases.

On admission the patient was in a good general condition, without fever, and he reported improved condition following the antibiotic therapy. The physical examination revealed reduced vesicular sound on the left, obesity and arterial pressure increased to 146/95 mm Hg. Gasometry demonstrated hypoxemia (PaO_2 60 mm Hg).

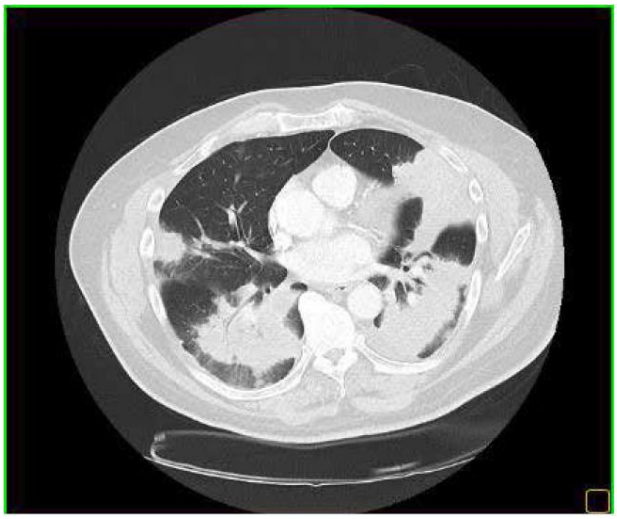

Figure 2. High resolution chest computed tomography. Massive consolidations with the air bronchogram, mostly in the middle and lower lungs between consolidations of visible ground-glass opacities.
Rycina 2. Tomografia komputerowa wysokiej rozdzielczości klatki piersiowej. W obu płucach rozległe nacieki miąższowe z powietrznym bronchogramem, zlokalizowane przede wszystkim w środkowych i dolnych partiach płuc. Między zmianami widoczne obszary zacienień typu szkła mlecznego.

Figure 3. Follow-up postero-anterior chest X-ray after a month of glucocorticoid treatment. Partial regression of the massive consolidations in the lungs.
Rycina 3. Kontrolne zdjęcie radiologiczne klatki piersiowej w projekcji tylno-przedniej wykonane po miesiącu leczenia glikokortykosteroidami. Częściowa regresja rozległych zagęszczeń miąższowych obustronnie w płucach.

IgA, IgM, IgG and IgE immunoglobulin concentrations were normal, carcinoembryonic antigen (CEA) level was at the upper limit of normal (4.70 ng/ml). The presence of HIV, HBV and HCV were excluded; *Mycoplasma pneumoniae* and *Legionella pneumoniae* infections were not confirmed. A slight elevation of the level of IgM antibodies against *Chlamydia pneumoniae* was observed (11.4; the normal range is <11). Cultures for tuberculosis and non-specific flora from the sputum and bronchoalveolar lavage were sterile, and in the fungal cultures *Candida albicans* 10^2 CFU/ml was grown. *Pneumocystis jiroveci* genetic material was detected in the bronchoalveola lavage from the patient. Echocardiographic examination revealed dilation of the ascending aorta, left ventricular hypertrophy, impaired LV relaxation, and signs of pulmonary hypertension (TVPG 37 mm Hg). Spirometry demonstrated reduced vital capacity (FVC 61%, FEV, 44% FEV/FVC 77%). The image of the bronchial tree from the bronchial fibroscopy was normal. A cryobiopsy and transbronchial lung biopsy were performed. Histological examination confirmed the presence of ongoing inflammatory process, with signs of organizing pneumonia.

The patient was diagnosed with OP, probable caused by *Pneumocystis jiroveci*, as well as pulmonary candidiasis, COPD, spontaneous arterial hypertension, and secondary pulmonary hypertension, obesity and nicotine dependency. The administered therapy included trimethoprim with sulfamethoxazole (980 mg t.i.d.), itraconazole (100 mg b.i.d.), prednisone (40 mg/d), ramipril (2.5 mg q.d.), amlodipine (5 mg q.d.), and formoterol in inhalations (9 μg b.i.d.). The therapy significantly improved the patient's condition, eliminated the fever and weakness, improved the gasometric blood parameters (PaO_2 69.5 mm Hg), pulmonary function (VC 84%, FEV_1 59%, FEV_1/ VC 69%, TLC 94%, RV 115%, DLco 91%), as well as resulted in a partial regression of the extensive parenchymal consolidations in the lungs (Figure 3).

The patient remains under the supervision of the Department of Lung Diseases, and the primary care clinic. He experiences a considerable improvement in his well-being. However, the treatment with glucocorticosteroids significantly impaired the control of concurrent diseases. Therapy of arterial hypertension required a modification. A fixed-dose combination of amlodipine 5 mg, indapamide 1.25 mg, perindopril 5 mg was used; in addition, nebivolol 5 mg and modified release doxazosin at a dose of 4 mg were prescribed. Metabolic disorders exacerbated visibly - body mass

increased (BMI 38 kg/m^2), steroid-induced diabetes developed, and lipid disorders persisted. Following a diet with a restricted intake of simple sugars and fats, and a recomendation of increased physical exercise; 1 g q.d. of extended-release metformin, and 10 mg q.d. of atorvastatin was introduced. The OP and COPD therapy was continued with good results.

Discussion

Respiratory tract infection, asthma and COPD are the most common respiratory diseases in the practice of a primary care physician. Interstitial lung diseases are very rarely diagnosed at the primary care level. Due to the non-specific symptoms, these conditions are difficult to detect, especially for primary care physicians, whose ability to order important additional tests, such as computed tomography, bronchoscopy or lung biopsy, is limited. Early diagnosis and introduction of proper treatment are of key importance for the prognosis; therefore, when interstitial lung disease is suspected, it is necessary to refer the patient for consultation with a pulmonologist, and to collaborate with the attending physician in the specialised centre.

The presented patient was diagnosed with secondary OP, probably caused by *Pneumocystis jiroveci.* These fungi are very common, and humans are their primary reservoir. In developing countries, over 80% of children under the age of 4 years old have specific antibodies against *Pneumocystis jiroveci* [8]. Pneumonia of this aetiology is the most common opportunistic infection in HIV patients [9]. Modern anti-retroviral therapy and routine chemoprophylaxis against *Pneumocystis* have reduced the incidence of these infections [10, 11]. Pneumocystosis is also observed in other patients with compromised immunity (transplant recipients, oncological patients, and patients with autoimmune disorders and using immunosuppressants) [9]. In the present case the above predisposing factors were not found.

Glucocorticosteroids are the treatment of choice in OP. They are commonly used due to their strong anti-inflammatory and immunosuppressive effects. However, the risk of adverse reactions increases with the dose and duration of the therapy. The most important adverse effects include: arterial hypertension, heart failure, diabetes, lipid disorders, ulcer disease, infections, osteoporosis, eye diseases, skin complications and neuropsychiatric disorders [12]. In the presented case diabetes developed, which required lifestyle changes and metformin therapy. The treatment of arterial hypertension and lipid disorders also had to be intensified.

The primary care physician plays an important role in the management of patients receiving long-term glucocorticosteroid therapy. As the most available specialist, general practitioner can quickly react to the complaints of patients regarding the treatment, and monitor for adverse effects.

In the present case, the COPD detected a few years earlier by a primary care physician was confirmed. However, the patient did not follow the recommended treatment, and only the diagnosis of OP, associated with significant hypoxemia and deterioration of respiratory function persuaded him to use inhalatory medications regularly. In the course of OP, functional lung tests demonstrated restrictive disorders specific for this disease, but along with the recovery process, the obstructive disorders typical for COPD were revealed, as confirmed by the results of the last spirometry (VC 97%, FEV_1 71%, FEV_1/VC 59%).

Conclusion

Rare interstitial lung diseases pose a challenge for primary care physicians, and only the close collaboration with specialised centres enables prompt diagnosis and proper management of patients.

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Locomotor system trauma and injuries in the army - causes and prophylaxis

Urazy i obrażenia narządu ruchu w wojsku – przyczyny i profilaktyka

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Abstract. Traumas in the military population constitutes an issue widely discussed in the literature. Military medical surveillance data is used to determine the types of trauma and their effects, i.e. injuries to the locomotor system. This data is a basis for working out prevention principles and enable monitoring the trends of change among military personnel. The results of the studies have suggested that carrying heavy loads by soldiers, participating in high intensity training programs and the type of footwear should be considered as significant trauma-causing factors leading to injuries and overload of lower limbs in military populations.
Keywords: injuries, prevention, soldiers

Streszczenie. Problem urazowości w wojsku jest zagadnieniem szeroko omawianym w piśmiennictwie. Dane z wojskowego nadzoru medycznego wykorzystywane są do określania zarówno rodzajów urazów, jak i ich skutków w postaci obrażeń lub uszkodzeń narządu ruchu. Dane te stanowią podstawę opracowania zasad profilaktyki i umożliwiają monitorowanie trendów zmian wśród personelu wojskowego. Wyniki badań wskazują, że za istotne czynniki urazowe, prowadzące do uszkodzeń i przeciążeń kończyn dolnych u wojskowych, uznawane są: przenoszenie dużych ciężarów przez żołnierzy, udział w programach treningowych o dużej intensywności oraz obuwie.
Słowa kluczowe: żołnierze, urazy, obrażenia, profilaktyka

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Military personnel serve many functions in the world and all these activities favour soldiers being physically fit for service and ending it safely. Post-traumatic injuries of the locomotor system may render these goals impossible to achieve. Traumas in the military are still a serious problem despite numerous studies devoted to them. The scale of the problem is reflected in the fact that in the American army traumas and injuries were the cause of 25,000,000 absences in just one year. Such high absenteeism means great costs, but also reduces the combat readiness of soldiers, which reflects the scale of the problem [1]. The occurrence of a trauma may significantly hamper the return to normal activity and generate costs related to work absence and rehabilitation. It was also pointed out that after sustaining an injury that resulted in locomotor system trauma, the risk of subsequent post-traumatic injuries increases [2-4]. A 13% increase in the frequency of lower limb injuries was indicated after previous ankle joint trauma [5].

The literature presents a wide range of studies related to injuries and traumas. Many authors have evaluated their risk factors in the military [2-6]. These works include both the most frequent injuries occurring in soldiers and the prevention thereof. Information on injuries and traumas in the army is taken from various sources. These sources can include data obtained directly from soldiers, as well a databases of military units or national databases [5, 7]. The Defence Medical Surveillance System (DMSS) is a central repository of all medical and outpatient contacts of American military personnel. The analysis of data from DMSS is necessary for the assessment of injury and trauma factors, and also for the monitoring of trends and setting priorities in trauma prevention. In order to create the database, the Americans use the ICD-9 code system developed by the World Health Organization (WHO). ICD-10 is the system currently applicable in Poland. Thanks to the use of the codes proposed by the system, it is possible to precisely mark each medical condition with a corresponding alphanumeric code. The

approach to public health in terms of preventing traumas in the military covers, first of all, use of the data in order to specify the severity of traumas and the scope of injuries [1]. Bruce Jones is one of the authors that systematically deals with this issue [1, 5, 8]. In one of his papers, he suggested procedures and methodologies to be implemented and adhered to in order to guarantee the systematic and effective prevention of traumas and to reduce the costs of injury treatment. The suggested basic stages include monitoring of information, and also specifying the risk factors and causes of traumas, as well as their outcomes. It also includes developing prevention programmes for individual troops on the basis of the results, implementing those programmes and assessing their effectiveness [1]. In his paper written in 2010 [1], Jones analysed data from 2000-2005. A total of 48.8% of the outpatients had lower limb injuries, of which 28.2% were knee joint injuries and 16.9% were injuries to the ankles and feet. As far as upper limbs were concerned, the post-traumatic injuries covered 18.4% of the whole, with most (12.3%) concerned shoulder injuries. The major causes of the traumas were various falls (17.5%), car and motorcycle accidents (15.4%), and sporting activities (13.1%).

Sports training is widely considered a significant factor causing damage to and strain of the locomotor system of soldiers [2, 4, 5, 7, 9-11]. In the case of people with low levels of activity, the main factors which cause trauma related to physical training are increasing loads too quickly, excessive running-induced loads, and inappropriate strength training [5, 10, 12, 13].

Traumas sustained by the various services were highly diversified in individual countries [5]. In all the discussed cases, the majority of injuries were found in the lower limbs [4, 5]. One of the most interesting observations made was that both part-time military personnel [5] and conscripts [4] were more likely to be injured or sustain trauma than full-time soldiers. The most typical injuries included: injuries to the ankle and shin joint, overload fractures, tendon inflammation, injuries to the iliotibial band, injuries to the patella, and lumbar spine pain [2, 5, 7, 10, 14, 15]. As soldiers are often diagnosed with traumatic injuries to the lower limbs, many publications suggest introducing modifications to their training. Reducing the number of long marches is suggested, as these have a cumulative effect, and a gradual increase in training intensity [2, 14, 16]. When the sleep time of the participants was maintained, the number of injuries decreased by 20% during check-ups [17]. The percentage of pelvic overload fractures sustained by female conscripts in the Australian Army during their one-year training preceding conscription into the army was analysed. One group underwent typical training, while for the other the marching pace was reduced from 7.5 km/h to 5 km/h. The runs took place on soft surfaces, with the tempo and step length being maintained, with the participants dispersed and not close to one another. Traditional medium-distance runs were replaced with interval training. As a result, the number of pelvic overload fractures was reduced from 11.2% to 0.6%. It was concluded that the modified training reduced pelvic fracture rate by limiting the frequency and the force of impact of training [18].

The basic training principles that must always be observed are the specifics of the training itself, the rest period and progressive overload [11, 19, 20]. Excessive loads and insufficient post-workout rest are not only factors which increase the risk of trauma, but can also cause sleep disorders, mental fatigue, changes in hormonal concentrations, and inflammatory lesions in muscles.

Inappropriate footwear is an important injury factor. Nevertheless, in research and in practice, footwear has often been disregarded as a factor which may cause injury, despite the many papers confirming the existence of this relationship [5, 9, 21]. Footwear can significantly impact one's movement pattern, which can, in turn, lead to overloading. It is the most important factor influencing the mechanics and kinematics of lower limbs. It can modify the manner one walks, contributing to a change in the movement pattern, thereby increasing the risk of injury [9, 21-23]. Military footwear should protect not only the foot but also the ankle joint. Even small changes in the dorsiflexion of the foot have a significant impact on the Achilles tendon. Ankle sprains are among the most common injuries to the lower limb [2, 5].

Other factors conducive to injuries include smoking, BMI, limberness, age, and gender. Smokers usually have a weaker musculoskeletal system and endurance than healthy fit individuals [13, 24, 25]. A BMI which is too high or too low is also regarded as one of the factors conducive to trauma. It is suggested that too-low BMI values are more dangerous, as they indicate muscle mass deficiencies, and often also bone mass deficiencies, which predisposes people to being more susceptible to locomotor system trauma [10]. Excessive BMI values have not been explicitly proven to cause an increased risk of trauma. The body fat percentage is a more important factor, with excessive values increasing the probability of trauma in men only [5]. The lack of limberness limits joint mobility and causes an increase in the number of muscle tissue trauma, whereas excessive limberness may cause joint dislocation, leading to their luxation [5]. Being very tall or flatfooted can increase the probability of overloading and injury [2, 5, 9]. It was determined that people with below-average 1-mile run results were more prone to injury than fitter individuals, which ultimately facilitated the conclusion that individual performance when starting military service is among the crucial factors [5].

Strength training loads can have a negative impact during strength training sessions due to performing too heavy lifts, as well as during military service, where solider load exceeds the allowed percentage of body

weight. The US Army differentiates 3 categories of soldier load: FL *(fighting load*), APL *(approach march load*) and EAML *(emergency approach march load*). When carrying a fighting load, the soldier carries only firearms and munitions. In the case of the approach march load, one can carry additional equipment weighing 21.7-32.7 kg and, in the case of the emergency approach march load, up to 54.5 kg. The anticipated daily distance is 20 km. The maximum weight of additional equipment should not exceed 45% of the soldier's body weight. As regards underweight people, the load exceeded 90% of their body weight, thus greatly increasing the risk of injury and the risk of overloading or trauma. When carrying such heavy loads, the soldier leans forward in order to maintain balance. This causes excessive strain of the lumbar spine [5]. Additional difficulties when marching with a heavy load include increased pace and slope. Increasing pace by 0.5 km/h or slope by 1% causes the same effect as adding 10 kg of load [26]. The most common injuries caused by excessive loads are blisters on the feet, metatarsal pain, knee pain, and lumbar spine pain. Special backpack hip belts are used to correctly distribute the load and to partially mitigate the adverse effects [5, 26].

Traumas sustained by people in service of the Armed Forces of the Republic of Poland can be evaluated based on data obtained from "The Information on the status of health and safety (of service) in the organisational units of the Ministry of National Defence in 2017" issued by the Social Affairs Department of the Ministry of National Defence [27]. A division into army employees and soldiers was applied. In 2017, a total of 5589 soldiers (5572 in 2016) were injured in activities associated with military service. The accident rate (measured as the number of individuals injured per 1000 soldiers in active military service) decreased in 2017 to 45.8 when compared to 48 in 2016. The highest accident rates were recorded in organisational units subordinate to the Armed Forces General Command (51.5), Military Gendarmerie Headquarters (48.4), and Warsaw Garrison Command (46.1). The lowest rate was observed in the organisational units of the Ministry of National Defence (4.3). Accidents were usually due to slipping, tripping, and falling, excessive physical or mental load, and moving on uneven terrain. The activities performed by the injured persons at the time of the accident included physical training (1657 accidents), moving (1472 accidents), driving means of transport (312 accidents), and carrying objects (275 accidents). The places where soldiers had accidents most often were sporting facilities (25.4% of all accidents), firing ranges (19.1%), staff buildings (10.4%), and transport routes within military units (8%). The injured soldiers most often sustained such injuries as limb dislocations and sprains or muscle tears (55%), wounds and superficial injuries (16.4%), and bone fractures (11%). The cited study did not take into account the percentage division between upper and lower limbs and other parts of the body. The presented national data confirmed the differences in the accident rate in various branches of services, which was also observed in the literature discussed above.

An appropriate injury prevention strategy is crucial given the significant number of injuries to the locomotor system and the associated treatment costs. The main objective of preventive measures is to extend the period in which soldiers can provide military service in full health, physical fitness and combat readiness. The objective of primary prevention is to reduce the probability of trauma and health problems, and to address factors which lead to such trauma and health problems. Injuries can be prevented through effective primary prevention activities. Basic military fitness tests should be extended to include the diagnostics of the soft tissues of the locomotor system and the correctness of movement patterns. This comprehensive evaluation should be first introduced for soldiers before entry into the special forces. Functional irregularities related to limited joint mobility or muscle tone asymmetries can contribute to functional disorders manifested at the various levels of the entire kinematic chain of the lower limbs and torso [28].

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Techniques of obtaining and saving X-ray images in field X-ray rooms – from the First Italo-Ethiopian War (1896) to the Second Iraqi War (2003)

Techniki uzyskiwania i zapisu obrazu rentgenowskiego w polowych gabinetach rentgenowskich – od wojny włosko-abisyńskiej (1896 r.) do II wojny irackiej (2003 r.)

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Abstract. The article describes problems related to obtaining X-ray images in field X-ray facilities during various theatres of war and how they were resolved, in the years 1896-2003. The introduction of digital image recording revolutionized the operation of field X-ray units and virtually eliminated the concept of a darkroom, which accompanied X-ray use since the very beginnings. It was the weakest link, seriously limiting the efficiency and mobility of X-ray facilities under field conditions.
Keywords: darkrooms, field X-ray room

Streszczenie. W artykule opisano trudności związane z zapisem obrazów rentgenowskich pod kątem działalności polowych gabinetów rentgenowskich na różnych teatrach działań wojennych i sposoby ich rozwiązywania w latach 1896-2003. Wprowadzenie cyfrowych zapisów obrazu zrewolucjonizowało działalność polowych gabinetów rentgenowskich, praktycznie eliminując pojęcie ciemni, która towarzyszyła diagnostyce RTG od chwili jej powstania. Było to zarazem najsłabsze ogniwo, silnie ograniczające wydajność i mobilność gabinetów RTG w warunkach polowych.
Słowa kluczowe: polowy gabinet rentgenowski, ciemnie

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Introduction

It was on 5 May 1894 that Wilhelm Conrad Roentgen ordered a Crookes–Hittorf electrical discharge tube with partial vacuum along with a Mueller-Unkelm power supply unit. A physicist and, since 1888, the physics chair at the Julius Maximilian University of Würzburg, Roentgen could not have predicted that he would soon become the founder of not only a new form of research methodology, but also a new medical specialisation [1]. Thanks to his sharp and enquiring mind, scientific curiosity and intuition, Prof. Roentgen discovered X-rays on 8 November 1895, and then managed to describe their properties within only 7 weeks of work. Moreover, his assessment of their potential was perfectly correct. In his experiments, he used a "dry plate" coated with a film (photographic emulsion) of silver bromide, invented by Richard Maddox in 1871. On 22 December 1985, following a 15-minute exposure process, the first X-ray image of a hand was presented to the world (Fig. 1). Roentgen also indicated that X-ray imaging or fluoroscopy may be of practical use in medicine. Carl Schleussner initiated the mass production of glass panels intended for use in X-ray imaging as early as in 1896. This was also the year when Thomas Alva Edison conducted a 3-month long study (from January to March) on the use of calcium tungstate (scheelite) in fluoroscopy. The resulting image was 6 times brighter than the barium platino-cyanide employed by Roentgen.

Field radiology continued to improve in terms of the methods, equipment and work organisation in field X-ray facilities over the course of multiple regional conflicts, to

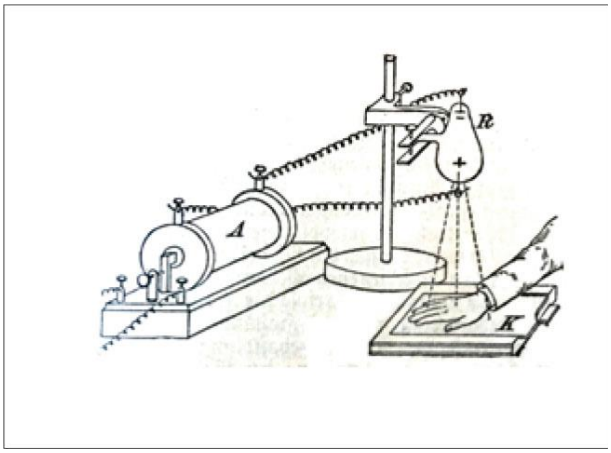

Figure 1. Radiography – first image taking set. A – Ruhmkorff induction coil, R – Hittorf-Crookes lamp, K – film cassette (source: Meyers Konversation - Lexikon, Leipzig und Wien 1909:3).
Rycina 1. Rentgenografia - pierwszy zestaw do wykonania zdjęć. A – cewka indukcyjna Ruhmkorffa, R – lampa Hittorfa-Crookesa, K – kaseta z filmem (źródło: Meyers Konversation – Lexikon, Leipzig und Wien 1909:3)

become an inherent element of battlefield facilities prior to the First World War. Due to the rapid development of science and technology, X-ray tubes were relatively durable by 1914, and the problem of a suitable power supply for X-ray equipment in field X-ray conditions solved. The use of this technology in regional conflicts before the First World War provided sufficient practical experience for X-ray diagnostics to be used on a massive scale, as seen from the sheer number of X-ray images produced by the French army in 1917-1918, which amounted to 100,000 [4]. However, a comprehensive system solution to the problem of capturing X-ray images under field conditions was only implemented 99 years later.

Regional conflicts preceding the First World War

Italian-Ethiopian War *(campagna d'Africa orientate)* (1894-1896)

The military usefulness of the X-ray camera was demonstrated on 19 January 1896 by the Viennese doctor Gustaw Kaiser. The X-ray image revealed the presence of pellets in the patient's soft tissue and a malunion of a gun-shot fracture in his forearm bone [3]. On 23 March 1986, Lt. Col. Giuseppe Alvaro MD, PhD used this new diagnostic method in two soldiers to locate bullets in the soft tissue of their forearms. Yet he was not the forerunner of field radiology, as the examination was performed 2 months after they were injured. It was conducted at the Military Hospital in Naples, to where the soldiers wounded in Abyssinia were evacuated [5]. Alvaro himself stated that "...the new technique has proved to be very helpful, allowing us to determine the position of the foreign body with mathematical precision" [6].

That publication contained a piece of undoubtedly invaluable information, i.e. a detailed description of the techniques used in X-ray imaging: "One takes a prepared photographic plate, places it in several layers of black paper, then puts it in a cardboard or wooden cassette, or on a small taboret in such a way that the impressed gelatinous surface is toward and underneath that part of the body of which the shadow is to be taken, it being fixed in this position with gauze. Above is placed the Crookes tube at a distance of 20 to 30 cm, the current being generated by a Ruhmkorff coil. After 20 minutes, or a good half-hour or longer, according to the potential of the current and the nature, thickness and density of the part, one obtains a negative with a relatively white shadow on a black base." [7, 8] This description clearly displays the technique and the material on which the image was captured as well as the procedure, which does not appear to be difficult, although very time consuming.

Greco-Turkish War (1897)

During the Greco-Turkish War, which lasted from 17 April to 4 December 1897, both sides to the conflict acquired radiological equipment and the medical personnel to use it via national Red Cross organizations [9]. Turkey was supported by Germany, who presented two X-ray devices to the hospital in Constantinople [10]. Greece was aided by England, France and Russia. On 13 May 1897, it received the very first X-ray apparatus produced by Miller & Woods Company in London [11].

Recording. The contribution of the British Red Cross was described in the "Daily Chronicle" newspaper in May 1897. The readers could learn that: "The apparatus forwarded will consist of an absolutely complete outfit in itself similar in every detail to the apparatus in daily use at St. Thomas' Hospital, London (...). It is hoped that it will

be possible to use the fluorescent screen to the exclusion of the photographic method, as the position of the bullet or the seat of the injury may be viewed in many positions rapidly, and the time required to develop a dry plate (although much shortened by the use of Eastman's new X-ray paper) constitutes a serious delay to a busy surgeon." The advantage of fluoroscopy was due to the fact that interpreting the image directly from the glass plates was significantly more problematic because of its low contrast. It was therefore sometimes resolved by copying the image from the glass plate onto light-sensitive photo paper (Eastman X-Ray paper), manufactured since December 1896 [12]. Under the field conditions in which the Greeks had to operate, an important part of the equipment was a large wooden cabinet to serve as a darkroom for image processing.

Tirah campaign (1897-1898)

In June 1897, the United Kingdom sent 4 corps consisting of 100,000 soldiers over the North-West Frontier between India and Afghanistan to quell an insurgency by Afghan tribes. One of these, the Tirah Expeditionary Force (TEF), consisted of 8,000 British and 30,000 Indian troops and was active in the province of Tirah. The TEF operated in a rather rural area, at a considerable distance from the hospitals in Rawalpindi, Nowshera and Kohat [13]. The TEF was the first unit to show the practical usefulness of the X-ray diagnostics under field conditions. The regimental surgeon, Surgeon-Major Walter Beevor, purchased all the necessary equipment at his own expense. In the course of combat activities, under field conditions, and sometimes under fire, Beevor examined 200 out of the 853 wounded soldiers (Fig. 2) [14].

He easily located projectiles and quickly assessed gun-shot fractures, making a huge impression on his superiors, General Hamilton and General Wodehouse (Fig. 3), who were also his patients.

The experience gained by the TEF confirmed that field X-ray services were extremely useful. Soon they became a permanent element of the British Army, and Major Beevor was promptly compensated for his private investment [15].

Recording. As in Greece, Eastman X-Ray paper and glass panels were used to capture X-ray images. Because of the high temperatures in the local climate, however, the latter proved to be problematic as the coating would frequently melt [15].

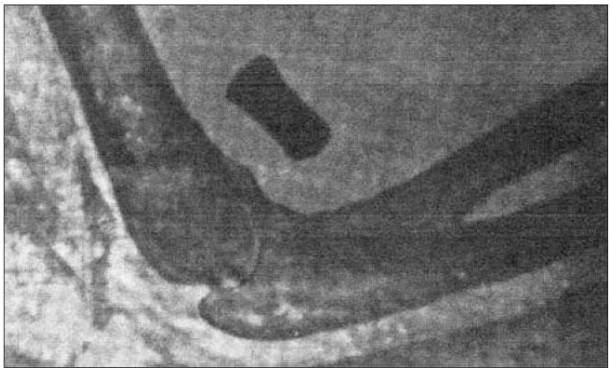

Figure 2. Bullet in elbow joint area. X-ray taken by the surgeon Major Walter Beevor [14]
Rycina 2. Pocisk w okolicy stawu łokciowego. Zdjęcie wykonane przez chirurga mjr. Waltera Beevora (źródło: 14. pozycja piśmiennictwa)

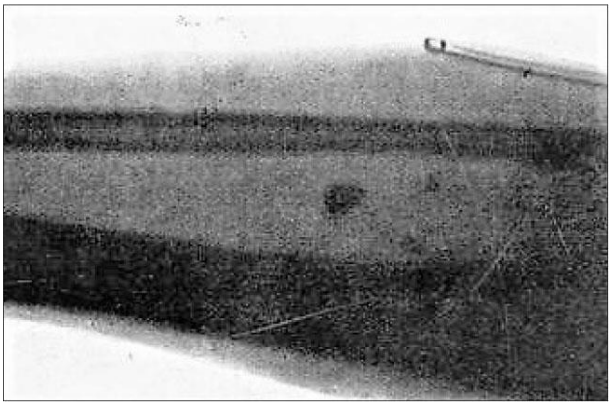

Figure 3. Bullet in General Wodehouse's shin. X-ray taken by the surgeon, Major Walter Beevor [14]
Rycina 3. Pocisk w podudziu gen. Wodehouse'a. Zdjęcie wykonane przez chirurga mjr. Waltera Beevora (źródło: 14. pozycja piśmiennictwa

Spanish–American War (1898)

The Americans began their experience with military X-ray diagnostics during the Spanish-American War, from 25 April to 12 August 1898. At the time the US entered the war with Spain, its army had 17 X-ray sets available. One apparatus was installed on each of the following Army hospital ships: "Relief", "Missouri" and "Bay State". As the combat operations were performed at sea (Cuba, Puerto Rico, Philippines, Guam), none of the X-ray cameras were used on land under field conditions at any time during the war. The results were described in the report for the Lower House of the Congress, i.e. the United States House of Representatives. It covered both the medical issues and the technical aspects of X-ray imaging [16]. The conclusion of the report indicated that radiation-induced skin damage is possible,

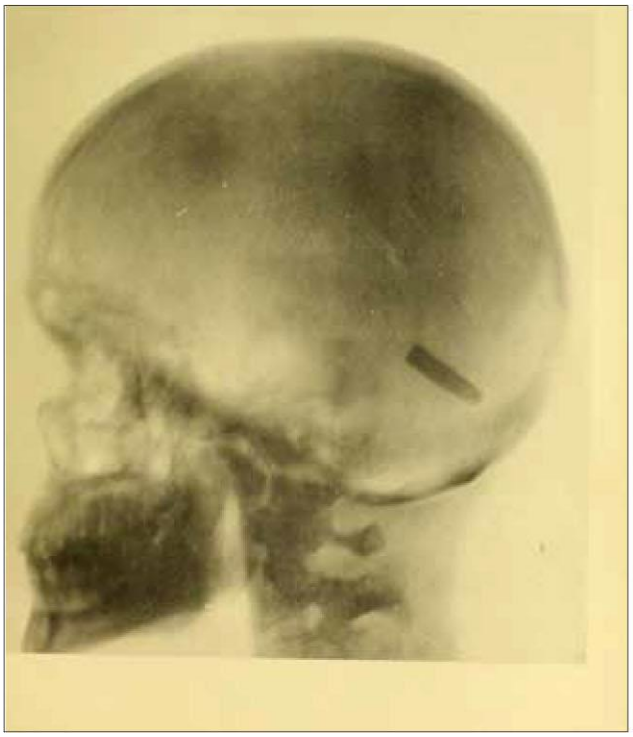

Figure 4. X-ray of a bullet lodged in the left occipital lobe of the brain of an American soldier in the Philippines. The solder was shot from a long distance in the Philippines in March 1899.
The picture was taken in August 1899 upon his evacuation to San Francisco [16]
Rycina 4. Rentgenogram pocisku tkwiącego w lewym płacie potylicznym u amerykańskiego żołnierza rannego na Filipinach. Żołnierz został postrzelony z dużej odległości w marcu 1899 r. Zdjęcie wykonane w sierpniu 1899 po jego ewakuacji do San Francisco (źródło: 6. pozycja piśmiennictwa) 16)

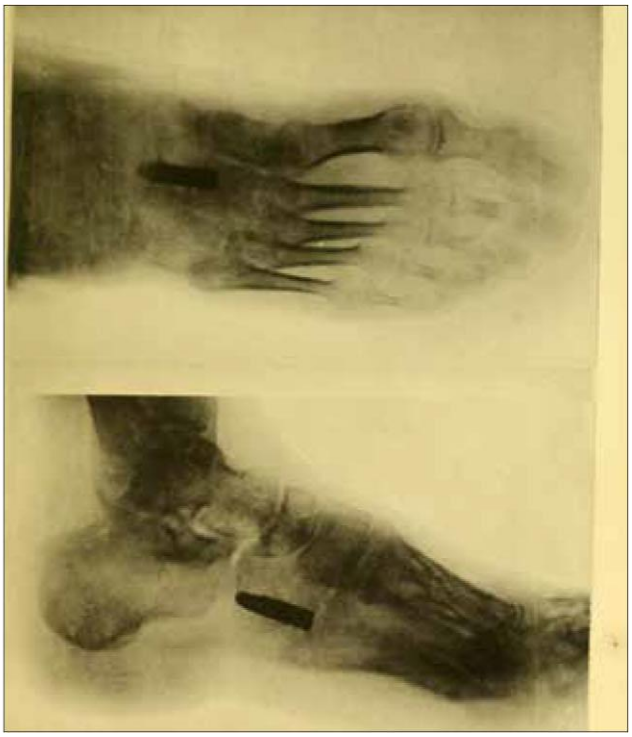

Figure 5. PA and lateral X-ray of left foot, showing a slightly deformed bullet embedded in the sole of the foot, beneath the cuboid bone and parallel with the second metatarsal bone [16]
Rycina 5. Rentgenogram lewej stopy, w projekcji A-P i bocznej, ukazujący nieznacznie zdeformowany pocisk, zlokalizowany w podeszwie stopy, pod kością sześcienną i równolegle do drugiej kości śródstopia (źródło: 16)

recommending that the maximum single exposure be no longer than thirty minutes and the distance between the X-ray tube and the body be not less than 10 inches (25.4 cm). The document stressed that longer time intervals are needed between successive exposures. The first standard exposure times were also presented:

- forearm and hand: 1-2 minutes,
- knee: 9 minutes,
- shoulder joints, chest: 10 minutes,
- pelvis, hips and skull: 20 minutes.

The content of the report proved that the wider public was still unfamiliar with the works of Michael Pupin, a Physics professor at Columbia University. In February 1896, by combining a standard fluoroscopic screen with a photographic glass plate in a single cassette, he shortened the hand X-ray exposure time to just several seconds! [12].

Since the X-ray rooms were used on hospital ships only, there was no problem in procuring suitable premises for a darkroom to process the X-ray images. The materials used for image capture were glass plates coated unilaterally with a thick emulsion of the highest light-sensitivity possible, produced by the Crammer Dry Plate Company, St. Louis. The report also draws attention to the relevance of the photographic paper (Eastman permanent bromide), invaluable in print-making (Fig. 4-5).

The long exposure times given in the report, as well as the issues related with comprehensive image processing, shows why fluoroscopy enjoyed such popularity in X-ray rooms from the very beginning, not only under field conditions, and especially with the use of a cryptoscope [6].

Sudan War / River War (1896-1897)

Providing X-ray diagnostics to the 25,800 Egyptian and 8,600 British troops of the Anglo-Egyptian Nile Expeditionary Force (NEF) was entrusted to Surgeon-Major John Battersby. For the first time, X-ray room equipment was issued by the British War Office as

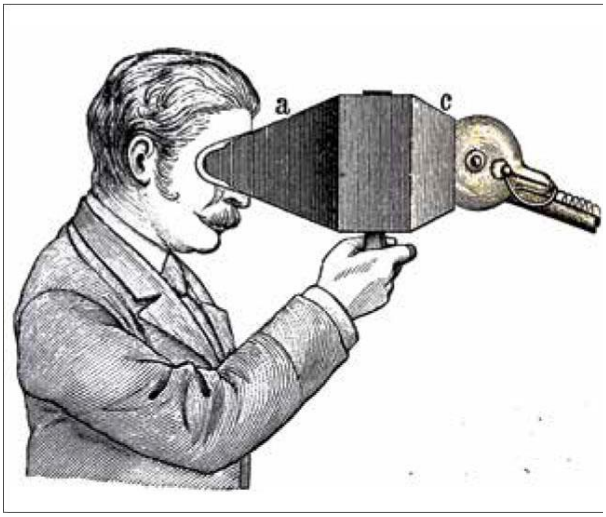

Figure 6. Cryptoscope (source: Meyers Konversation - Lexikon, Leipzig und Wien 1909:3).
Rycina 6. Kryptoskop (źródło: Meyers Konversation - Lexikon, Leipzig und Wien 1909:3).

part of the regular medical supply for the NEF. Bearing in mind the weather conditions, i.e. high temperatures in Sudan, ranging from 37.8° to 50°C, the photo materials were secured already at the planning stage. They were transported in wooden boxes covered in felt and kept moist at all times. This ensured a maximum temperature inside of 29.4°C. All these efforts were most reasonable since the later descriptions of work in X-ray rooms in Sudan indicated heat and dust as the main difficulties [17].

Recording. The use of the glass plate coated with an easily melting gelatine emulsion to capture the image required the personnel to wait until 03.00 hours, when the temperature in the darkroom constructed from sun-dried bricks fell to 33-43°C. Another problem were the dust storms, which penetrated the darkrooms. The dust would stick to the hot emulsion covering the plate, which can be seen still on archived images.

The essential disadvantages of using glass plates under field conditions were: high cost, fragility and weight (20 times greater than that of the X-ray film). These issues connected with combat operations conducted in hot climates proved to be a problem for field X-ray conditions during the Second World War as well.

Boer war (1899-1902)

Throughout the Second Boer War (11 October 1899 – 31 May 1902), the usefulness of radiology under field conditions was tested and well documented for the very first time. So was the power of both the German Mauser and UK Lee-Enfield rifles, which used cartridge ammunition on a large scale, reducing the small arms calibre to less than 10 mm. Iron bullets drastically changed the nature of gunshot wounds, and thus their treatment. The wounds were clean and the entry and exit holes smaller, yet the higher speed of the projectile caused a new problem: necrosis surrounding the tissues surrounding the bullet's wound track (temporary cavity) as well as secondary wound infections, not observed previously in the era of soft lead bullets. 556,653 soldiers served in the British Army over the course of the Boer War. It was the first test for the Royal Army Medical Corps, established a year before the outbreak of the conflict, in terms of its treatment and evacuation capacities. Both parties were already enjoying the benefits and possibilities of X-ray diagnostics. The Boer had 5 devices at their disposal: in Jacobsdal, Springfontein, Krugersdorp, Johannesburg and Pretoria. The British had 10, including those on hospital ships. The "British Medical Journal" of 1899 even described the standard supplies of a field X-ray facility, including "...chemical reagents, photo paper and 108 Edwards (glass) plates".

Recording. It was still highly problematic to develop and fix the image on the radiograph. This was primarily due to the weather conditions in South Africa. These required the following:

- a suitable darkroom to develop the plates – the images had to be developed at night because of the sunlight passing through the fabric of the tent,
- sufficient water to wash and fix the images, deficient in the dry Karu desert,
- suitable temperatures for image processing, as the summer heat made the emulsion melt on the glass plates,
- a dustproof darkroom, because the ubiquitous dust and sand would stick to the emulsion coating of the glass plates [19].

It should be stressed that X-ray images were developed in trays until 1900. There were no standards established for the development of plates or for the chemical reagents employed. Consequently, every picture had to be processed individually. It was only about 1906 that the first wooden containers with grooves to store vertical glass plates appeared in the darkroom. The exposure of X-rays and difficulties in processing still encouraged many to use the shorter and easier method instead, i.e. fluoroscopy with the use of a cryptoscope [6]. This proved fatal to the pioneer of British radiology, Dr John Hall-Edwards. After 14 months, having examined 280 patients (multiple times in many cases), he had to

return to England in order to have his left forearm and all the fingers of his right hand amputated due to X-ray dermatitis [19].

First Balkan war (1912-1913)

Lasting from 8 October 1912 to 18 November 1913, the First Balkan war was the last test for the X-ray imaging before the "Great War". The solutions applied at that time were soon creatively improved by Maria Skłodowska-Curie. She supervised the construction of French mobile X-ray ambulances. That war saw a wider application of motor vehicles for the transport of equipment (in cases), which allowed for a greater mobility of X-ray rooms. These mostly encompassed permanent components (Fig. 7) [20, 21].

Recording. From 1910, it was a common practice to use containers or tanks instead of trays. They had bars fitted to the top edge of the image instead of grooves, allowing the X-rays to be suspended vertically in the solution. This simple idea not only facilitated the transfer of radiographs to subsequent tanks, but also led to standardisation of the tank size.

First World War (1914-1918)

Mobile X-ray units during the First World War

With the automotive industry developing rapidly, horse-traction was gradually being replaced by motor vehicles in many military formations. As for X-ray diagnostics, the rapid move from horse-carriages would not only improve the mobility of field X-ray rooms, but also allow the vehicle engine to be used to generate power for the apparatus.

Maria Skłodowska-Curie

As early as in the first weeks of the war, Maria Skłodowska-Curie (1867-1934), the director of the Red Cross Radiology Service, was authorised to construct mobile X-ray units by Gen. Joffre. Thanks to her authority as a distinguished scientist, she managed to collect funds for the construction of a dozen X-ray units using the chassis of Renault passenger cars and trucks (Fig. 8).

The first two "Radiologie" cars drove to the front lines on 1 November 1914, headed for the field hospital in Crecil, near Compiegne. To summarise the military accomplishments of radiological services, Marie Skłodowska-Curie wrote the manual "Radiology and War", issued in 1921 [22].

Figure 7. 1st Balkan War - a vehicle for transporting equipment for the mobile X-ray room [21]
Rycina 7. I wojna bałkańska - samochód przewożący wyposażenie mobilnego gabinetu radiologicznego (źródło: 21)

Recording. In 1912, David Bowen standardised the process of X-ray image development based on a system of 4 tanks, each used for a different treatment: capturing, washing, fixing, final rinse and drying (Fig. 9) [4].

The time frame of the process was soon standardised as well, with a fixed time for the radiograph being captured at a constant temperature of the developer solution maintained by means of a thermostat.

The shortage of glass panels became an issue at the very beginning of the war, when Germans occupied Belgium – a major global manufacturer of those supplies. Fortunately, this problem was solved very timely for the Allies by a US company called Kodak. In 1913, it launched an X-ray film based on cellulose nitrate. A combustible material, it allowed for coating the film with emulsion on both sides. There was no risk of parallax, as opposed to the thick glass plates. However, this was not mass-produced until 1918, although such a system was already recommended in 1897 by Max Levy. Glass plates and film were used simultaneously or interchangeably throughout the entire war. It was only around 1920 that glass started to be considered obsolete [4], partly an effect of the introduction of (non-combustible!) cellulose acetate into X-ray imaging in 1921, which was preceded by several large fires in hospital X-ray archives due to self-ignition.

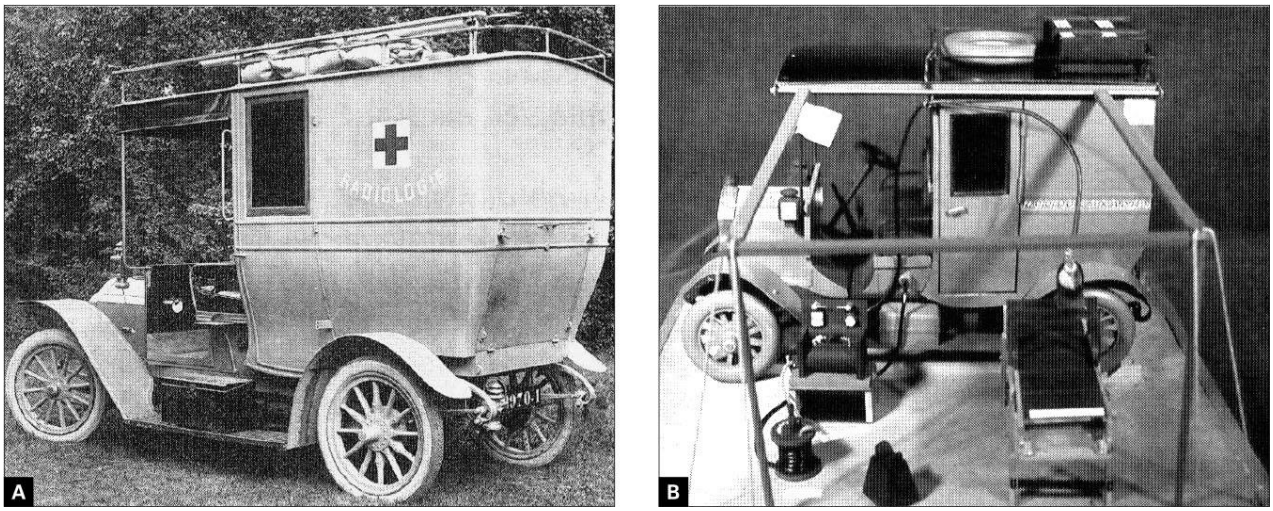

Figure 8. French X-ray ambulance with a darkroom on its way (A) and ready to use (B) [21]
Rycina 8. Francuski ambulans rentgenowski z ciemnią w drodze (A) oraz rozwinięty (B) (źródło: 21)

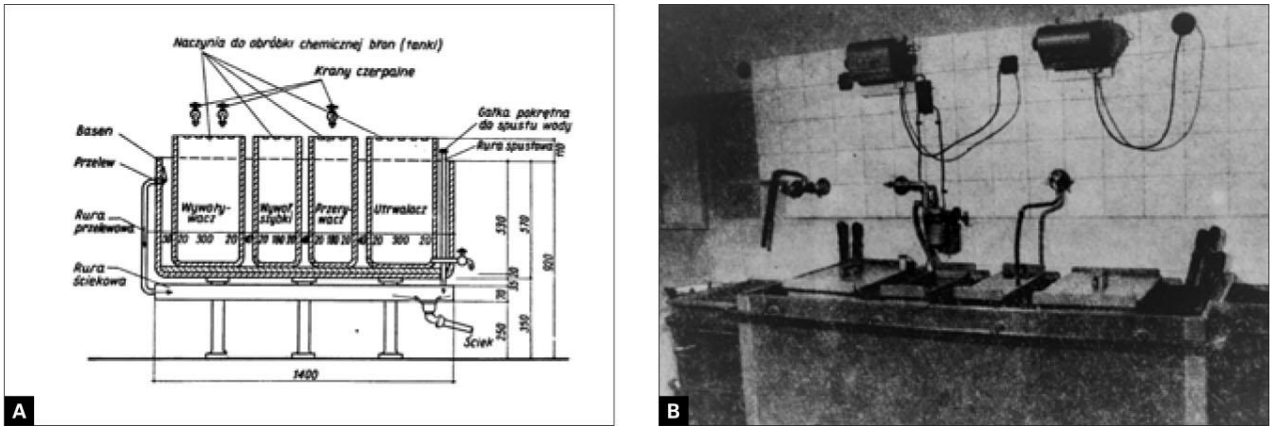

Figure 9. A. Diagram of process line with a set of containers for developing X-ray pictures in a manual darkroom. **B.** Manual darkroom - a set of containers for developing X-ray pictures (source: authors' collection).
Rycina 9. A. Schemat ciągu technologicznego z układem pojemników do wywoływania rentgenogramów w ciemni ręcznej. **A.** Ciemnia ręczna z układem pojemników do wywoływania rentgenogramów (źródło: materiał własny).

Military radiology in the US Army 1917-1919;

When the Americans entered the war in 1917, they had little experience in the organization of radiologic services or the construction of field X-ray rooms. The previous time was for use on hospital ships when they were fighting Spain in 1898. The difficulties experienced by the Greeks in trying to ensure power supplies for X-ray apparatus during the war with Turkey in 1897, as well as the struggles of the UK in the Tirah valley, where the British medical base came under fire while a projectile was being removed under fluoroscopic guidance, led the Americans to conclude that X-ray apparatus would not be used effectively in the vicinity of the front line. Consequently, they assumed that the use of X-ray apparatus in mobile hospitals was not justified and should be limited to stationary hospitals or hospital ships. They claimed that "...a projectile in a wound rarely requires immediate removal." This view gained so much traction among policy makers that the U.S. Army and U.S. Navy did not have a single field X-ray apparatus on joining the war on 6 April 1917. This belief clashed with reality during the First World War, and the experience they gained was aggregated in the U.S. Army Division 1918 manual published in 1918. It contained many practical tips and information on field radiology.

Recording. Colonel Christie, who was in charge of the X-ray equipment for the U.S. army on the Western Front, compared various types of mobile X-ray units in the following words: "The advantage of the English and

French camions over the American one is that the two former have the body of the car arranged as a dark room, while the latter is not. Experience in this war has shown that the greater part of the X-ray work in hospitals in forward areas, including evacuation hospitals, is fluoroscopic. The few plates that will be made can conveniently be developed in the small portable dark room furnished with the American apparatus" [23].

Second World War (1939-1945)

Col. Christie's remarks regarding no need for installing darkrooms in vehicles fell on deaf ears. On the eve of the Second World War, they became standard equipment for mobile X-ray units in most European armies.

Recording. The transfer of images between tanks in the process of chemical treatment and drying was further facilitated by the introduction of Kodak metal frames for film mounting in 1918 [24].

The system was relatively simple. By the end of the Second World War, the standard equipment of a field darkroom consisted of tanks and frames, although portable darkrooms were still in use in ad hoc situations to reload the cassette and capture the film, just like during the First World War. Kodak did not develop a market version of the automatic processing equipment until 1956. It could develop 6 films per minute, as the film was transported on a series of rollers. This device was, however, far from mobile, as it weighed 750 kg and was up to 3 meters in length.

Regional conflicts following the Second World War

Korean War (1950-1953)

In Korea, medical security covered five levels or echelons of evacuation. X-ray diagnostics was incorporated in the third of these levels – the Mobile Army Surgical Hospitals (MASH). It was only here that the injured received surgical help rather than having just their vital functions maintained. This was also a critical element of medical evacuation which determined the successful healing and evacuation [25]. The X-ray equipment used at the beginning of the war in MASH was from the Second World War period. The doctrine was based on the experience of that war – it focused principally on the methods of locating missiles or shrapnel as well as the assessment of gun-shot fractures. Techniques that had been used for a long time, i.e. fluoroscopy and radiography, were sufficient to that end. However, the large-scale implementation of vascular surgery in MASH called for significantly better equipment capabilities. It was the new operating techniques that triggered the modernisation of both X-ray apparatus and image recording. While the X-ray apparatus underwent fairly quick standardisation, darkrooms were still an issue.

Figure 10. Xeroradiogram of a skull phantom dipped in a paraffin block. Parameters of exposure: 50kV/100mAs with a distance of 70 cm (source: authors' collection))
Rycina 10. Kseroradiogram fantomu czaszki zatopionej w bloku parafinowym. Wartości ekspozycji: 50kV/100mAs przy odległości 70cm (źródło: materiał własny)

Recording. Image processing still involved tanks and frames, just as during the Second World War. The only new element to accelerate this time-consuming process were 2.5 kW electric dryers.

The introduction of dryers was the only remedy that could reduce the processing of X-ray pictures. It often happened that the wounded soldier received an initial diagnosis in MASH and was qualified for a rapid helicopter evacuation, while the radiograph was not properly fixed or dried yet, and hardly legible upon reaching the higher level of medical evacuation. The helicopter was the real revolution in medical evacuation. Highly flexible, it showed how archaic the darkroom equipment of field X-ray rooms had become. At first, Polaroid seemed to be the opportunity for change. Launched in 1948, this camera system employed a special cassette with photo paper instead of film. This allowed the pictures to dry within 60 seconds without any human intervention. However, the images obtained did not meet the quality parameters, so the project was discontinued [26]. Another technique which sparked some hope at that time was xeroradiography, an imaging process developed by Dr. Robert C. McMaster in 1950 where the picture was recorded on paper rather than on

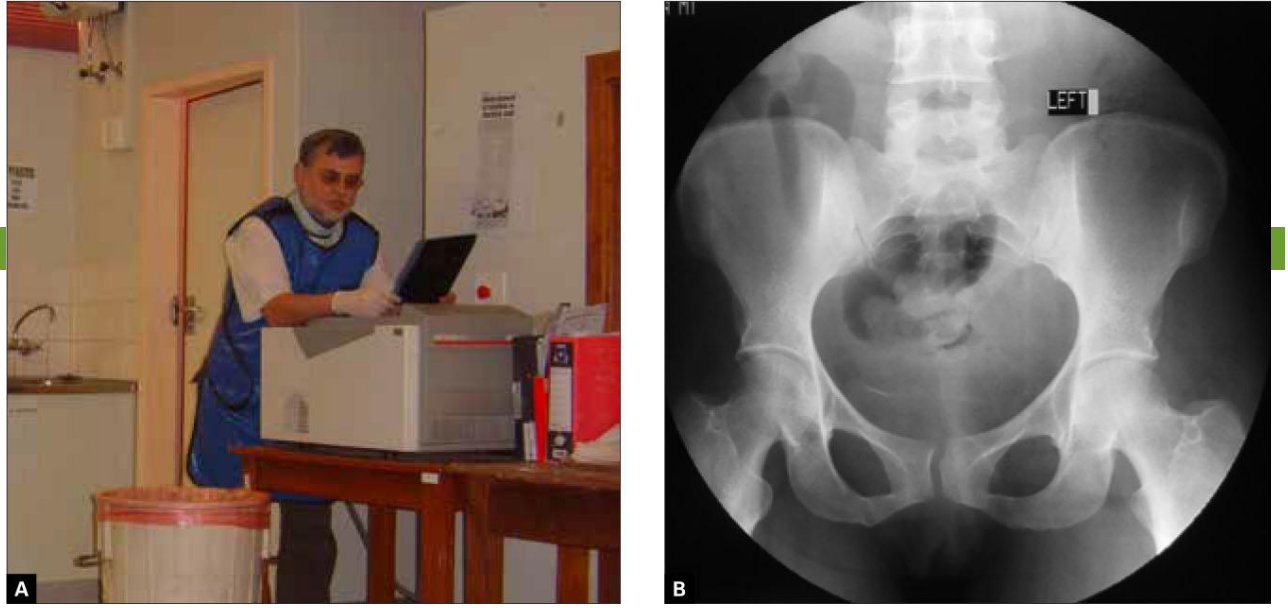

Figure 11. A. DRYSTAR1000-laser printer recording images on the radiograph film. Department of Diagnostic Radiology and Imaging University of Limpopo-MEDUNSA, Polokwane, RSA/RPA, Apr. 2004. **B.** The image of the X-ray saved on the film by a laser printer (source: authors' collection).
Rycina 11. A. DRYSTAR 1000 -drukarka laserowa do zapisu obrazu na kliszy/filmie. Departament of Diagnostic Radiology and Imaging University of Limpopo -MEDUNSA, Polokwane, RSA/RPA, kwiecień 2004. **B.** Obraz zapisany na kliszy przez drukarkę laserową (źródło: materiał własny).

film (Fig. 10). With the exception of a short period in xeromammography, this method did not receive substantial acclaim. These devices, a product of the USSR, were still a part of mobilization equipment of the Polish Army in the 1990s.

A breath of fresh air came in 1951 with the electronic image amplifier, which allowed for conducting fluoroscopy in daylight thanks to the transfer of the image onto a monitor screen (real-time radiography), while the radiation dose was reduced by 25% [27]. With the high brightness of the image on the screen, it also became possible to directly record it with an analogue system, i.e. intermediate telerecording. It was replaced with VCR in 1956 and with a laser printer in 1984 **(Fig. 11).**

Vietnam war (1957-1975)

Severe weather and geographic conditions along with the threat of guerrilla attacks on land transport forced the US Army to evacuate the wounded from combat using helicopters. This was possible owing to the absolute domination of the U.S. Air Force in the air. The widespread use of helicopters allowed for the evacuation of the injured directly from the battlefield to hospitals located in large military bases or on hospital ships along the Vietnam coast. These were equipped with extensive treatment and diagnostic facilities and numerous medical personnel.

Recording. Since the X-ray diagnostic equipment was located in large bases, it was possible to use even the largest automatic image processors: "X-Omat". By 1960, there were already 200 of them in use in the USA – yet there is no information that this was the case. The personnel of SAA "Sanctuary" (AH-17), which had 3 X-ray devices on board, as shown on a video recording, also used "wet" photo development techniques, i.e. tanks and frames. Perhaps the price and the size of the device were not the only reason. An automatic processor did not eliminate the necessity of a darkroom completely. It was still required to load a clear film into the cassette, to remove the exposed film from the cassette and to put it into the automatic processor. It was therefore of no significant importance that polyester was introduced as a substrate for the production of X-ray images in 1960, although it allowed the increase in the developer solution temperature up to 36°C, so that the darkroom processing lasted only 90 seconds. It was only in 1975 that the first automatic table film processor, the AGFA Gevamatic 60, was launched. This change came too late, since its introduction coincided with the end of the Vietnam War.

Figure 12. AGFA Curix 69 automatic developer on the transport box in darkroom container. Polish Field Hospital of the Polish Military Contingent in the Stabilization Force in the Republic of Iraq. Camp Lima near Karbala, 2004-2008 (source: authors' collection)
Rycina 12. Wywoływarka automatyczna AGFA Curix 69 postawiona na skrzyni transportowej w kontenerze-ciemni. Polski Szpital Polowy Polskiego Kontyngentu Wojskowego w składzie Sit Stabilizujących w Republice Iraku, Camp Lima k. Karbali, 2004-2008 (źródło: materiał własny)

Figure 13. In the corner - small automatic darkroom on board assault ship USS "Bonhomme Richard" (LHD-6), Persian Gulf, May 1991 (source: R. Łochowski - by permission)
Rycina 13. W rogu widoczna mata ciemnia automatyczna na pokładzie doku desantowego USS „Bonhomme Richard" (LHD-6), Zatoka Perska, maj 1991 (źródło: R. Łochowski -za zgodą)

Despite its small and compact size, as well as low weight (approx. 40 kg), it had an essential disadvantage – the processor table needed to be levelled exactly first. It also still required a darkroom, but at least it demonstrated a new quality and was quickly adopted in hospitals and hospital ships, as shown by the presence of the AGFA Curix 69 automatic processor in the Polish Field Hospital in Iraq, in the Camp Lima base near Karbala, over the years 2003-2008 (Fig. 12). This device was previously used in a French field hospital, forwarded to the Polish Army in the 1990s.

Gulf War (1991)

Combat operations were carried out by the coalition forces under the command of the US and lasted from 17 January to 28 February 1991. In the peak period, the U.S. Army had 44 hospitals, consisting of Mobile Army Surgical Hospitals (MASH), Combat Support Hospitals (CSH), as well as hospital ships and hospitals in South-Eastern Asia [25].

Operation Desert Storm

Operation Desert Storm demonstrated the need for more mobile medical facilities. Despite the minimal medical losses observed, the increased scale of the injuries called for more radical action. Moreover, combat units underwent an organizational change towards a system of BCT (brigade combat team), UEx (future division/corps and UEy (future corps/army). The high mobility of these units required a rapid increase in medical unit mobility. This process was initiated when CSH units were singled out from the Medical Reengineering Initiative (MRI).

Recording. In automatic table darkrooms at that time (Fig. 12), equipped with new chemical reagents and materials used in the manufacture of the X-ray film, the radiograph development process lasted 45 seconds. Devices of this type were found not only in field hospitals, but also on hospital ships (Fig. 13).

Introduced in 1984, laser printers were the first of the new methods of image fixing (Fig. 14).

Figure 14. Laser printer on board assault ship USS "Bonhomme Richard" (LHD-6), Persian Gulf, May 1991 (source: R. Łochowski - by permission)
Rycina 14. Drukarka laserowa na pokładzie doku desantowego USS „Bonhomme Richard" (LHD-6), Zatoka Perska, maj 1991 (źródło: R. Łochowski -za zgodą)

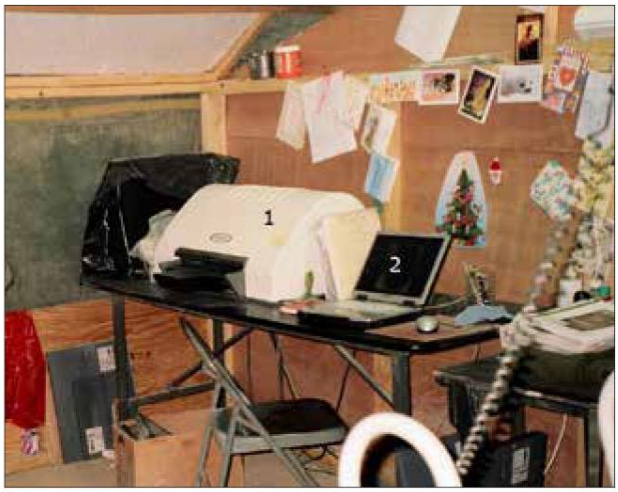

Figure 15. Field X-ray room in FST – Camp Babylon. (1) PcCR 1417 ACL4. (2) Computer/RTG (images screen 12 Dec 2003) (source: authors' collection)
Rycina 15. Polowy Gabinet RTG w FST – Camp Babilon. (1) PcCR 1417 ACL4. (2) Komputer/monitor obrazów RTG (zdjęcie wykonane 12.12.2003) (źródło: materiał własny)

Iraq War (2003)

This war encompassed three-week combat operations from 20 March to 1 May 2003, followed by the formal occupation of Iraq to 2005.

Recording. From the point of view of field radiology, this war was a real breakthrough to the Israeli company OREX Ltd, founded in 1995. Initially active in digital X-ray imaging used in dentistry, it shook up the market with a portable device to scan images with the use of cassettes with phosphor plates. The device, named PcCR 1417 ACL4, completely revolutionised the process of archiving X-ray images in field conditions (Fig. 15). It was not only the size of the device (L-100, FJ-80, H-50 cm) or its weight (40 kg) that allowed it to be placed on a simple field table. What was truly new was that the X-ray image appeared on the monitor screen in less than 1 minute without the need for a darkroom, chemicals, dryers etc! It operated smoothly across the temperature range of 18-30°C and maximum humidity up to 80%. As air conditioners were already in widespread use in Iraq, it was easy to use. A substantial benefit was that the system was compatible with the X-ray equipment used before. The fact that the first order by the U.S. Army amounted to 250 units shows how much it was anticipated.

Conclusion

The historical perspective on all the predicaments, barriers and difficulties which accompanied the recording of radiologic images from the moment of its arrival through all military deployments until the introduction of PcCR 1417 ACL4 should suffice to dismiss any allegations regarding covert advertising of the device.

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18F-PSMA-1007 - a breakthrough in PET/CT prostate cancer imaging? A systematic review

18F-PSMA-1007 PET/CT - przełom w obrazowaniu raka gruczołu krokowego? Przegląd systematyczny

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Abstract. Early diagnosis of relapsing prostate cancer is one of the most important factors determining patient survival. Positron emission tomography/computed tomography (PET/CT) is successfully utilized in this setting. Studies show that prostate-specific membrane antigen (PSMA) radiotracers, especially those labelled with fluorine 18 (^{18}F), seem to have the highest specificity and sensitivity among other prostate cancer tracers. In this systematic review the authors present a current state of the art of PET/CT imaging using 18F-PSMA-1007, a radiopharmaceutical which in the papers published to date showed the best pharmacokinetic and pharmacodynamic properties, and the highest diagnostic sensitivity in relapsing prostate cancer patients.
Keywords: fluorine 18, PET/CT, prostate cancer, prostate-specific membrane antigen, PSMA

Streszczenie. Wczesna diagnostyka wznowy ma kluczowe znaczenie dla przeżycia pacjentów z rakiem gruczołu krokowego. Pozytonowa tomografia emisyjna/tomografia komputerowa (PET/CT) ma w tym kontekście klinicznym mocno ugruntowaną pozycję. Jak wykazują badania, największą czułością i swoistością cechują się radioznaczniki celowane na antygen błonowy stercza (PSMA). Wśród nich natomiast największy potencjał mają te znakowane fluorem 18. W niniejszym przeglądzie systematycznym autorzy przedstawiają aktualny stan wiedzy na temat PET/CT z wykorzystaniem 18F-PSMA-1007, radiofarmaceutyku, który w dotychczas opublikowanych badaniach wykazywał najlepsze właściwości farmakokinetyczne i farmakodynamiczne oraz największą czułość diagnostyczną u pacjentów ze wznową raka gruczołu krokowego.
Słowa kluczowe: PSMA, antygen błonowy gruczołu krokowego, fluor 18, rak gruczołu krokowego, PET/CT

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Introduction

Positron emission tomography/computed tomography (PET/CT) using prostate-specific membrane antigen (PSMA) radiotracers has an established position in prostate cancer (PCa) imaging, in particular in patients with biochemical relapse (BCR), who require disease re-staging. Moreover, in this group of patients the PSMA-targeted radiotracers demonstrate the highest sensitivity and specificity. Studies show that PET/CT test using ^{68}Ga-PSMA-11 (presently the most extensively tested tracer for prostate-specific membrane antigen) detects the site of PCa recurrence in up to 50.0 - 57.9% of patients with BCR and very low PSA concentrations (<0.5 ng/ml) [1, 2]. The method's high sensitivity is also noteworthy. It was demonstrated that the result of a PET/CT test with ^{68}Ga-PSMA-11 tracer may change the treatment in up to 76% of patients.

However, imaging diagnostics using radio-pharmaceuticals labelled with galium 68 (^{68}Ga) has considerable disadvantages. ^{68}Ga-PSMA-11 is

eliminated through the kidneys, so the radioactive urine collected in the bladder impairs the assessment of the prostate, the bed following its removal and the adjacent structures. Moreover, the availability of the ^{68}Ga isotope is quite limited. A ^{68}Ge/^{68}Ga generator produces only 2-4 isotope doses per day, and its short half-life (approx. 68 minutes) prevents its effective transportation over long distances. As a result, ^{68}Ga can be used only in facilities that have their own generators [4, 5]. The fluorine 18 (^{18}F) half-life is approximately 110 minutes, so it can be produced in cyclotrons in large quantities, and then transported even to distant research facilities [4]. PET images with ^{18}F-labelled radiotracers also demonstrate a superior resolution compared to ^{68}Ga [6]. The favourable pharmacokinetic and pharmacodynamic profile of fluorine 18-labelled PSMA radiotracers explains their increasing popularity in PET/CT imaging. The systematic review below presents the current state of knowledge about 18F-PSMA-1007 - a radiotracer from this group that appears to be the most promising.

Methods

The authors carried out a review of the PubMed database, searching for the key words: “prostate cancer”, “PSMA”, “1007” and “PET”. A total of 17 works published in the years 2017-2018 were found, of which (following perusal of the abstracts) 4 were rejected as not meeting the subject criteria. The full text of the remaining 13 publications (4 retrospective studies, 3 pilot studies, 3 case reports and 3 pre-clinical studies, involving approximately 400 patients in total) was analysed, and included in this review. This article also contains preliminary data from an ongoing study with the use of 18F-PSMA-1007 PET/CT conducted by the authors.

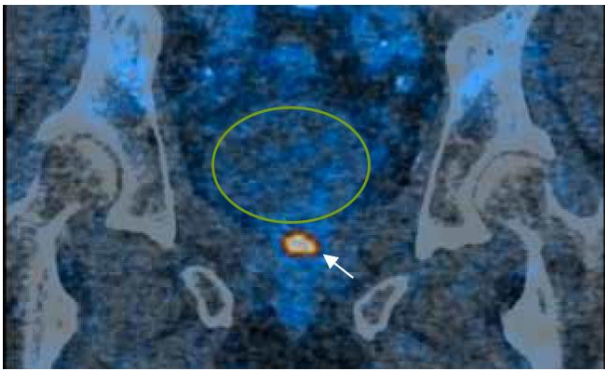

Figure 1. A 77-year-old patient with PCa after radical prostatectomy, androgen deprivation therapy and radiotherapy (due to local relapse). Currently the patient shows biochemical recurrence with PSA levels rising to 1.4ng/ml. 18F-PSMA-1007 PET/CT scans show tracer-avid local relapse (white arrow), SUV_{max} =9.2. Noticeably, urinary bladder (within green circle) shows minimal radioactivity. A radiocholine PET/CT performed two months earlier was negative - the site of local relapse was not visible, presumably due to the overlapping radioactivity within the bladder (authors' own material).
Rycina 1. 77-letni pacjent po radykalnej prostatektomii, hormonoterapii i radioterapii z powodu wznowy miejscowej PCa (7 lat temu). Obecnie wznowa biochemiczna (stężenie PSA 1,4 ng/ml). W badaniu 18F-PSM A-I 007 PET/CT widoczne jest ognisko wznowy w loży pooperacyjnej (biała strzałka), SUV_{max} =9,2. Uwagę zwraca brak gromadzenia znacznika w pęcherzu moczowym (obrysowany zieloną linią). W wykonanym dwa miesiące wcześniej PET/CT z radiocholiną ognisko nie było widoczne, najprawdopodobniej z powodu nakładającej się na nie radioaktywności z pęcherza moczowego (materia) własny).

Results

The 18F-PSMA-1007 radiotracer was developed and synthesised for the first time in 2016 by scientists from Heidelberg, Germany. Similarly to the majority of the presently studied PSMA tracers, 18F-PSMA-1007 is a small molecule PSMA inhibitor whose urea group binds with the active centre of the enzyme. When the ligand (tracer) binds with the enzyme (PSMA), the ligand-enzyme is internalised, and trapped inside the cell [7]. Therefore, the cells with PSMA overexpression (prostate cancer cells) are visible in the PET/CT test as places with increased tracer uptake (metabolically active) [4, 8]. 18F-PSMA-1007, like other tracers in this group, also accumulates in healthy organs: kidneys, lacrimal and salivary glands, liver, brain, testicles, ovaries, intestines and healthy prostate. As PSMA expression in these tissues is clearly reduced compared to the PCa cells, the uptake of the radiopharmaceutical agent is correspondingly smaller [4, 9]. The feature that distinguishes 18F-PSMA-1007 from other small molecule PSMA inhibitors is its favourable elimination mechanism. 18F-PSMA-1007 is excreted with the urine, but due to the temporary tracer retention in the renal parenchyma, its infiltration into the urine is delayed. Therefore, trace radiation amounts are found in the urinary bladder: at 0-2 hours after dose administration it is 1.2% of the administered dose, and at 4-6 hours it is approximately 0.5% of the administered dose. The doses absorbed by the urinary bladder are minimal. Limited accumulation of the radiotracer in the bladder enables a precise assessment of the prostate and the surrounding tissues, which in the case of other tracers in this group is associated with a significant margin of error (Figure 1) [5.10].

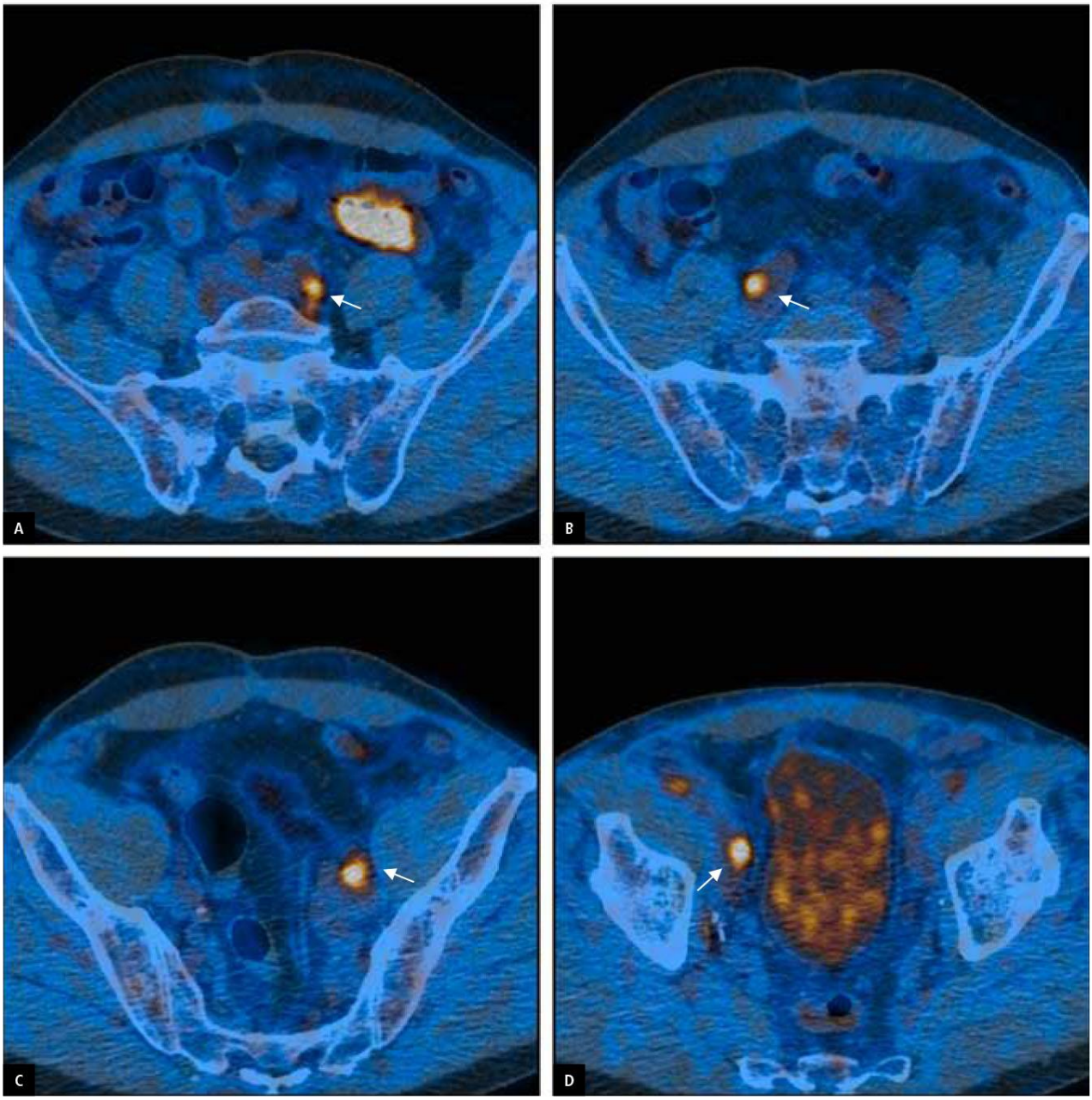

Figure 2. A 69-year-old patient with PCa after radical prostatectomy, lymphadenectomy and radiotherapy of the postoperative organ site (2 years ago). Currently the patient shows biochemical recurrence with PSA levels of 0.155 ng/ml. 18F-PSMA-1007 PET/CT scans show non-enlarged (7-10 mm in short axis), metastatic lymph nodes along the common and external iliac arteries bilaterally (A-D, arrows), SUV_{max} up to 4.1. Radiocholine PET/CT performed a month earlier did not show neither local nor metastatic disease (authors' own material).

Rycina 2. 69-letni pacjent po radykalnej prostatektomii, limfadenektomii i radioterapii na lożę pooperacyjną (2 lata temu). Obecnie wznowa biochemiczna (stężenie PSA 0,155 ng/ml). W badaniu 18F-PSMA-1007 widoczne są aktywne metabolicznie przerzuty do niepowiększonych węzłów chłonnych (7-10 mm w osi krótkiej) biodrowych wspólnych i zewnętrznych obustronnie (A-D, strzałki), SUV_{max}do 4,1. Wynik wykonanego miesiąc wcześniej badania PET/CT z radiocholiną był ujemny — nie uwidoczniono aktywnej metabolicznie wznowy miejscowej ani przerzutów PCa (materiał własny).

18F-PSMA-1007 is administered intravenously, in a single dose injection of 250-380 MBq [5]. In patients with PCa the neoplastic lesions are visible 40 minutes after administration. However, the tumour-to-background ratio (TR) improves with time, and appears to be optimal after 2-3 hours following the injection [4, 5]. Rahbar et al. demonstrated that accumulation of the tracer in the liver also increases with time, which may impair the assessment of potential hepatic metastases [11]. In the research centre in Heidelberg, where the highest number of PET/CT tests using 18F-PSMA-1007 is performed, imaging is conducted 90-120 minutes after the administration of the tracer [12, 13]. The greatest number of publications evaluating the usefulness of 18F-PSMA-1007 in prostate cancer focuses on patients with BCR. It has been demonstrated that PET/CT imaging with the use of this tracer reveals pathological lesions in 81-95% of patients. Even very small lesions are visible, e.g. metastases in non-enlarged lymph nodes (Figure 2) [5, 12, 13]. As is the case with radiocholines and other PSMA tracers, the sensitivity of PET/CT using 18F-PSMA-1007 is considerably determined by the patients' PSA concentrations [12, 13]. At the concentration of >2 ng/ml, it is 94-100%. In patients with very low PSA concentrations (<0.5 ng/ml) the detection rate is still relatively high, reaching 61-85% [12, 13]. To compare, radiocholines (presently the most common tracers in the diagnostics of BCR) at such low PSA levels demonstrate detection rates of 12% (Figure 2) [14]. In the study conducted by the authors with the use of 18F-PSMA-1007 the detection rate for suspected recurrence lesions in patients with BCR and PSA concentration of <2.0 mg/ml was 52% (data based on 23 patients, i.e. 58% of the target group). It should be emphasised that early diagnosis of PCa relapse is of key importance for further patient management. It has been demonstrated that rescue radiotherapy is most beneficial in patients whose PSA levels do not exceed 0.5 ng/ml - the six-year biochemical relapse-free survival in this group is 48%. When PSA concentration is higher, in the range of 0.51 - 1 ng/ml, 1.01 - 1.5 ng/ml and >1.5 ng/ml, the six-year survival decreases to 40%, 28% and 18%, respectively [15]. Apart from PSA levels, the detection of pathological lesions in 18F-PSMA-1007 PET/CT tests increases with malignancy of the primary tumour, as assessed by the Gleason grading system, and the use of antiandrogen therapy [12]. The limited accumulation of 18F-PSMA-1007 in the urine enables a relatively precise assessment of the prostate, post-operative bed and the surrounding tissues. Although multiparametric magnetic resonance imaging (mpMRI) remains the method of choice in the assessment of local PCa advancement and suspected local relapse, there are individual reports indicating that 18F-PSMA-1007 PET/CT may be at least equally effective in this setting [16, 17]. Freitag et al. demonstrated that PET/MRI with the use of 18F-PSMA-1007 may also be used successfully in the primary evaluation of PCa staging [18]. The group of small molecule PSMA inhibitors is constantly expanding to include new compounds that could potentially be used in the future in PCa imaging. To date, 18F-PSMA-1007 and ^{18}F-DCFPyL dominate in this group with respect to the number of patients tested, and the diagnostic value of the examination. Both compounds demonstrate identical sensitivity. However, 18F-PSMA-1007 enables a better assessment of the lesser pelvis, due to limited accumulation of the tracer in the urine, whereas ^{18}F-DCFPyL accumulates to a lesser degree in the liver, so it appears to be better suited for patients with advanced disease and possible hepatic metastases [19]. The absence of histopathological analysis of the lesions detected in PET/CT tests is a significant limitation of the studies presented in this article. However, it should be emphasised that the size of the detected lesions is decreasing, which considerably complicates the biopsy procedure and further microscopic assessment. A study by Giesel et al., in which lesions detected in 18F-PSMA-1007 PET/CT tests were verified in a histopathological examination, demonstrated that the correlation between a positive PET/CT result and the presence of PCa cells in the analysed samples is very high - the sensitivity of imaging was 97.4% [5].

It is also worth mentioning that the currently available data on 18F-PSMA-1007 are obtained primarily from retrospective and pilot studies or case reports, and refer to a limited number of patients.

Conclusions

According to the studies published to date, 18F-PSMA-1007 PET/CT is presently a very good (if not the best) tool for the diagnostics of biochemical relapse of PCa in patients with low PSA concentrations. Due to the easy production, high availability, very good image quality and beneficial pharmacokinetic and pharmacodynamic profile of the radiotracer, its use will certainly increase. Hopefully, along with the growing number of patients tested with this method, the body of publications (especially prospective studies) on this subject will also increase and enable a full understanding of the benefits and shortcomings of this promising radiopharmaceutical agent.

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Travel medicine for divers

Medycyna podróży dla nurkujących

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The presented article is a fragment of the monograph by Jarosław Krzyżak and Krzysztof Korzeniewski *Medicine for Divers*, which is to be published in 2019 by Agencja 4Font in Poznań.

Abstract. All over the world, there has been a sudden increase in the number of international journeys, mostly for tourist-related purposes. Of the growing number of travellers, those who are also recreational divers is also increasing. Many popular places for diving are located in tropical and subtropical areas (Red Sea, Mediterranean Sea, Caribbean Sea, Indian Ocean, and Pacific Ocean). An essential part of pre-travel arrangements of divers include their health status assessment during medical consultation, preparing all the necessary medications for chronic illnesses and a travel first-aid kit for personal use, vaccinations, antimalarial chemoprophylaxis, and travel insurance covering the entire travel and not only the times spent underwater.
Keywords: diving, prophylaxis, travel medicine

Streszczenie. Na całym świecie obserwowany jest znaczący wzrost liczby podróży zagranicznych, głównie w celach turystycznych. Do zwiększającej się populacji podróżnych należą również nurkujący rekreacyjnie. Wiele popularnych miejsc do nurkowania znajduje się w rejonach tropikalnych i subtropikalnych (Morze Czerwone, Morze Śródziemne, Morze Karaibskie, Ocean Indyjski, Ocean Spokojny). Istotnym elementem przygotowań do wyjazdu osób nurkujących jest ocena ich stanu zdrowia podczas wizyty lekarskiej, dobór leków dla osób przewlekle chorych oraz leków do apteczki pierwszej pomocy do wykorzystania we własnym zakresie, przyjęcie szczepień ochronnych, przygotowanie chemioprofilaktyki przeciwmalarycznej oraz ubezpieczenie, które będzie dotyczyło całej podróży, a nie tylko momentów zejścia pod wodę.
Słowa kluczowe: nurkowania, medycyna podróży, profilaktyka

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Introduction

In the last decades, interest in recreational diving has risen spectacularly. As many popular diving sites are located in tropical and subtropical destinations, it would be a reasonable decision to take certain preventive measures before travelling to countries characterised by challenging environmental conditions, in order to reduce the risk of health problems.

It is important to remember that diving is associated with the risk of health damage, or even death. However, by following suitable psychological and physical preparations, and respecting safety precautions while underwater, this sport offers unforgettable experiences, incomparable to the time spent on land. Before travelling to a planned diving destination, appropriate preparations should be made, covering not only contact with the aqueous environment, but also the fauna and flora on land. Therefore, a consultation with a physician, protective vaccinations and antimalarial chemoprophylaxis, the contents of the first-aid kit and insurance will apply to the entire trip, not only the time spent underwater.

The most important elements of preparation for the journey include the assessment of health status and choice of drugs for chronically ill patients and the pharmaceuticals for the first-aid kit, to be used at the discretion of the travellers. One should seek consultations in medical centres offering knowledge and experience not only in the field of hyperbaric medicine, but also tropical and travel medicine.

Medical advice

The first task is to determine the current psychophysical status of the traveller, and potential contraindications for diving. All people who are planning

to dive, especially those who are attempting it for the first time, should undergo a thorough physical examination (especially of the respiratory system, cardiovascular system, upper respiratory tract, ears and the mental status). The information regarding history of diseases is also important [1]. Particular attention should be paid to patients receiving treatment due to respiratory diseases (bronchial asthma, COPD), diseases that can potentially lead to consciousness disorders (diabetes, epilepsy), mental disorders (anxiety) or cardiovascular diseases (arterial hypertension, coronary disease) [2].

People who practice recreational diving for many years should undergo periodic examinations to confirm their current psychophysical status. The World Recreational Scuba Training Council, www.wrstc.com, introduced guidelines for physical examinations to determine psychophysical ability and for absolute contraindications for diving. The guidelines were approved by the Divers Alert Network (DAN), www.diveralertnetwork.org, and by the Undersea and Hyperbaric Medicine Society, www.membership.uhms.org [3].

Assessment of the health status of divers, and especially of candidates for diving, should include their age and sex. People over 50 years old should be aware of their limited physical fitness, and potential contraindications due to various diseases and received drugs. As for children, there are no formal age-based contraindications in place, although it is accepted that the minimum age for recreational diving is at least 12 years old, provided the physical examination confirms sufficient fitness and physical strength for carrying the aqualung, emotional maturity to operate in the underwater environment, and absence of health-related contraindications. In healthy women the only contraindication for diving is pregnancy. If a woman experiences tension headaches during menstruation, abstaining from diving in that period should be considered [1].

The group of recreational divers includes a number of people suffering from chronic diseases or using pharmaceuticals for chemoprophylaxis that are not considered to be contraindications for the hyperbaric state. However, attention should be paid to certain drugs that may be contraindicated. Patients who have started using new medications only recently should monitor their status for adverse events and report any to their doctor, who can then modify the treatment [4-6]. The comments regarding use of certain drugs by divers are presented in Table 1.

According to DAN, cardiovascular diseases are the second most common cause of death in divers, following drowning, so particular care should be exercised to ensure proper treatment and prophylaxis in cardiac patients [7]. Mild and moderated bronchial asthma, with normal spirometric parameters, is not a contraindication for diving [8]. The guidelines regarding contraindications for diving in a diabetic state include that the patient must use adjusted, constant insulin doses for at least 12 months, and oral antidiabetic medications for at least 3 months, their glycosylated haemoglobin concentration must be < 9%, and have no history of hypo- or hyperglycaemic episodes within the past 12 months [9].

A patient attending a medical consultation before a planned trip needs to prepare the relevant information regarding the activities associated with diving, as well as be prepared to discuss other topics related to the stay in certain destinations. To provide optimal medical preparation for the planned journey, the physician needs to obtain the data regarding the travel itinerary (country, region, altitude, climatic conditions, sanitary standards), travel duration, the planned departure and return dates, type of accommodation at the destination (comfortable hotels, low-budget hostels), types of activity apart from diving (sunbathing, high altitude climbing, caving), previous immunoprophylaxis (standard vaccinations, booster vaccinations and revaccinations) and received antimalarial chemoprophylaxis, presence of food allergies, allergies to drugs, cosmetics or chicken egg white (a compound of vaccines), chronic diseases, currently used medications and present diseases, being a carrier of infectious diseases, compromised immune system or pregnancy [10-12].

Diving-related morbidity does not differ significantly from the incidence of conditions caused by other forms of physical activity. The incidence of decompression sickness is estimated to be 5-80 cases per 100 thousand dives [13]. The estimated risk of death among the members of the American and European Divers Alert Network is 1/6000 dives per year. To compare, the risk of death related to jogging is 1/7700 people per year. Drowning is the official cause of death related to diving; however, the greatest challenge for the medical services dealing with underwater medicine include problems with the use of air and breathable gas mixes, too rapid surfacing, and patients with diseases in which a hyperbaric environment is contraindicated [7, 14].

Table 1. Selected medications and their possible adverse effects on divers
Tabela 1. Wybrane leki oraz ich możliwe działania niepożądane u nurkujących

Medications	Comments
Narcotics/analgesics	Narcotics - contraindicated; NSAIDs - no contraindications
Cardiac	Certain hypotensive drugs may reduce tolerance to physical effort
Insulin	Glucose levels should be controlled before each dive
Antidepressants	Contraindicated
Anticonvulsive drugs	Contraindicated
Antimalarial drugs	Mefloquine - contraindicated; doxycycline, atovaquon/proguanil - no contraindications
Sympathomimetics	Pseudoephedrine may reduce the risk of ear barotrauma
Anti-motion sickness medications	Have sedative effect, reduce the activity of CNS
Antidepressants	Have sedative effect, reduce concentration and slow the decision making processes
Data based on 2 positions in the references.	

Obligatory and recommended vaccinations

Following the World Health Organization (WHO) guidelines, preventive vaccinations against two infectious diseases are obligatory in international tourism. The first one is directed to Muslim pilgrims going to Saudi Arabia (vaccination against meninogococcal infections), the other one - against yellow fever - is obligatory for tourists travelling to 28 African countries where the disease is endemic, and 13 countries in South and Central America, as well as for people staying in these countries (even if only as part of a 12-hour transit), and then going on to the 90 countries across 5 continents mentioned in the WHO guidelines [15]. The remaining vaccinations have a status of recommended immunisations (Table 2).

Yellow fever

The risk of infection with the yellow fever virus is 10 times higher in Africa than in South America (Table 3). In western Africa infections are the most frequent in the late rainy season and early dry season (July-October). In South America, the highest disease transmission is observed in Brazil and Peru (the risk of infection is increased especially during the rainy season, from January to March). In unvaccinated tourists the risk of developing a severe form of the disease, resulting in death, during a 2-week stay is 1:2,000-1:10,000 in Africa, and 1:20,000-1:100,000 in South and Central America [16].

Meningococcal infections

Meningococcal infections are observed across the world. 5-10% of the general population may be carriers of the aetiological factor in invasive meningococcal disease (IMD) - the *Neisseria meningitidis* bacteria. Epidemics break out primarily in large population centres (Muslim pilgrims in Saudi Arabia), and in closed environments (dormitories, military barracks and prisons). Particularly high incidence is observed in the countries of Sahelian Africa (so-called meningococcal belt) between Senegal and Ethiopia, in the dry season from November to June [17].

Cholera

WHO estimates the global incidence of cholera at over million infections and 21-143 thousand deaths per year. In April 2017, the greatest cholera epidemics broke out in Yemen: by 07/10/2018, over 1,236 million new cases, including 2,556 deaths, were reported [18]. In the last decade, the greatest number of cholera cases was reported in Haiti, where over 813 thousand new cases, including 9,676 deaths, were observed since the outbreak of epidemics in October 2010 until August 2017 [19]. The greatest exposure to *vibrio cholerae* is observed among travellers visiting the countries where the disease is endemic and epidemic in Africa (e.g. Kenya, Tanzania), Asia (Yemen, India, Nepal) and the Caribbean (Haiti, Dominican Republic) who do not follow the principles of food hygiene [17].

Table 2. Vaccinations recommended in countries popular among divers
Tabela 2. Szczepienia ochronne zalecane w krajach popularnych wśród nurkujących

Country	Yellow fever	Meningococcal infections	Cholera	Typhoid fever	Type A hepatitis	Type B hepatitis	Diphtheria	Rabies	Japanese encephalitis
South-East Asia									
Philippines			Z	Z	Z	Z	Z	Z	Z
Indonesia			Z	Z	Z	Z	Z	Z	Z
Malaysia			Z	Z	Z	Z	Z	Z	Z
Thailand			Z	Z	Z	Z	Z	Z	Z
Indian Ocean									
Andaman Islands (India)				Z	Z	Z			
Maldives				Z	Z	Z			
Mauritius				Z	Z	Z			
Seychelles				Z	Z	Z			
Pacific Ocean									
Fiji				Z	Z	Z			
Palau				Z	Z	Z			
Central America and Caribbean Islands									
Belize				Z	Z	Z		Z	
Cayman Islands				Z	Z	Z			
Costa Rica				Z	Z	Z		Z	
Mexico			Z	Z	Z	Z	Z	Z	
Red Sea									
Egypt				Z	Z	Z	Z	Z	
Mediterranean Sea									
Croatia					Z	Z			
Greece					Z	Z			
France					Z	Z			
Spain					Z	Z			
Italy					Z	Z			
Malta					Z	Z			
Tunisia					Z	Z		Z	

Z - recommended vaccinations
Source: www.medycynatropikalna.pl (based on the WHO and CDC 2018 guidelines and recommendations)

Typhoid fever

Typhoid fever is a cosmopolitan disease. The risk of infection is increased primarily in regions with low standards of food preparation hygiene. Water reservoirs contaminated with waste water, e.g. due to a breakdown of the water supply and sewage disposal network system, also pose a hazard. The global prevalence of typhoid fever is estimated at 21 million people per year, and in over 220 thousand cases the outcome is fatal [15]. The greatest risk of developing the disease is observed in the developing countries of Asia, Africa, South and Central America. 80% of all the new cases globally are reported in

Table 3. Countries with endemic areas of yellow fever
Tabela 3. Kraje endemicznego występowania żółtej gorączki

Continents	Countries
Africa	Angola, Benin, Burkina Faso, Burundi, Chad, Democratic Republic of the Congo, Ethiopia Guinea, Guinea Bissau, Equatorial Guinea, Gabon, Gambia, Ghana, Kenya, Congo, Liberia Mali, Mauritania, Niger, Nigeria, Central African Republic, Senegal, Sierra Leone, Sudan, Soutl Sudan, Togo, Uganda, Ivory Coast
South and Central America	Argentina, Bolivia, Brazil, Ecuador, Guyana, French Guyana, Colombia, Panama, Paraguay Peru, Surinam, Trinidad and Tobago, Venezuela

Source: based on 17 positions in the references.

South Asia (Bangladesh, India, Pakistan, Nepal), South-East Asia (Vietnam, Laos), and China. Preventive vaccinations together with proper food hygiene are dedicated to travellers who intend to eat street food while visiting South and South-East Asia, as well as the developing countries [20].

Hepatitis A

Hepatitis A is a cosmopolitan disease; the level of endemicity of the infection varies in different geographical regions, and is associated primarily with poor sanitary and hygiene conditions. The risk of hepatitis A infection increases while visiting regions with low food hygiene standards, where travellers intend to have meals at the local market [21].

Hepatitis B

Hepatitis B is a cosmopolitan disease; WHO estimates that 257 thousand people across the world are infected with the HBV virus. In 2015, 887 thousand people died due to hepatitis B, mostly due to complications such as cancer or cirrhosis. The highest rates of HBV infections are reported in Africa and Oceania (over 6% of the adult population), in Middle East, Central Asia and North-East Africa (3.3% of general population), and in South-East Asia (2.0% of general population) [15]. Risk factors for HBV infection during travel include contact with infected blood or other body fluids. The risk is increased particularly in the case of occasional sexual encounters or injections (medications, narcotics). While staying in the regions where the disease is endemic, one should avoid occasional sexual encounters or intentional breaking of tissue integrity (piercing, tattoos [22].

Diphtheria

Diphtheria is a cosmopolitan disease. Despite ongoing efforts, numerous new cases are reported in South Asia (India), South-East Asia (Indonesia, Laos, Burma), and East Africa (Madagascar). In 2015, 4,530 cases of diphtheria were detected across the world (including 2,365 in India and 1,627 in Madagascar). In 2016, the incidence increased in India (3,380) and in Madagascar (2,865) [15].

Tetanus

Wound infection with tetanus spores can be observed in any region of the world, especially in the developing countries. Numerous cases of tetanus infection are found in South Asia (India, Nepal, Bangladesh, Pakistan), South-East Asia (the Philippines, Vietnam) and East Africa (Kenya, Uganda). In 2015, 10,337 cases of tetanus were detected across the world (including 2,268 in India and 1,804 in Uganda). In 2016, the incidence increased in India (3,781), Kenya (2,776) and the Philippines (1,082) [15].

Rabies

The disease is usually spread when an infected animal bites or leaves its saliva on the injured skin or mucosa of a person (the virus is transmitted with the saliva of the sick animal). It is estimated that approximately 55,000 people per year die due to rabies. The main source of infection (approx. 95% of cases in humans) are dogs, less often cats, bats and wild predators. The highest incidence of rabies is observed in India (approximately 20 thousand per year), and in other countries in South and South-East Asia (Afghanistan, Pakistan, Bangladesh, Nepal, Burma, Cambodia), and in Africa (Democratic Republic of the Congo, Burkina Faso, Niger, Nigeria, Ethiopia, Somalia, Kenya, Tanzania and Mozambique) [15].

Japanese encephalitis

Japanese encephalitis is transmitted in 22 Asian countries, and in two countries in Australia and Oceania (Papua-New Guinea, Australia, York Peninsula, Queensland). WHO estimates that 68 thousand new cases occur annually, of which several thousand are fatal. As in most cases the disease is asymptomatic, only some of them are diagnosed and reported. In 2016, new cases of Japanese encephalitis were reported in 17 countries - 5,399 cases in total. The highest incidence was observed

in India (1,627), Bangladesh (1,294), China (1,130), Burma (393), Vietnam (357) and the Philippines (312). The risk of developing Japanese encephalitis is increased in the rural areas and wetlands that are breeding grounds for mosquitoes, vectors for the infection [15].

Antimalarial chemoprophylaxis

Malaria is a parasitic disease, caused in people by five Plasmodium parasites: *Plasmodium falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi.* People are infected as a result of a bite by an infected mosquito (introducing invasive *Plasmodium* forms to the blood), through transfusion of blood containing *Plasmodium* trophozoites or schizonts, or by vertical route from mother to foetus. The protozoan parasite Plasmodium that causes malaria lives in the human liver and red cells of the peripheral blood. Malaria is transmitted by female mosquitoes of the *Anopheles* genus. The infection vectors in the malaria regions usually live at altitudes up to 2000 meters above sea level (with the exception of certain parts of Afghanistan, Bolivia, Ethiopia, Eritrea, Kenya and Pakistan, where cases of disease transmission at 2200-2500 m above sea level are reported). Three billion people live in 95 countries in regions where malaria is endemic. According to WHO, in 2015 a total of 214 million people suffered from malaria (88% in Africa, 80% in 17 countries, and 40% in only three countries: Democratic Republic of the Congo, Nigeria and India). In this period 438 thousand of deaths were reported (90% in Africa, 70% among children under 5 years of age, 80% of cases in 14 countries, and 47% in six countries: Nigeria, Democratic Republic of the Congo, Tanzania, Uganda, Mozambique and Ivory Coast). The most common aetiological factors of the infection are *P. falciparum* and *P. vivax* (80-95%). In well-developed countries (North America, Western Europe), approximately 10 thousand infections are reported annually, imported from the regions of disease occurrence, primarily from Sub-Saharan Africa and South-East Asia. Occasionally, cases of “airport malaria” or “port malaria” are observed, i.e. Infections in the airport or port area in the countries where the disease does not occur, but the infection vectors (mosquitoes) are transported to the moderate climate zone on planes or ships [17]. In recent years, cases of indigenous malaria in Europe were reported in Greece in 2013; in 2016 individual infections among Greeks were seen again (12 communes from Thessaloniki to the Peloponnese are at risk of disease transmission) [23].

In Poland, 20-30 patients a year are diagnosed with malaria and treated for the disease, imported from the regions where it is endemic.

Malaria prevention covers a range of measures, including:

- regular use of antimalarial medication (atovaquon/proguanil, doxycycline, mefloquine or chloroquine),
- use of individual personal protection: mosquito net, repellents (with 30-50% DEET [N,N-diethyl-*meta*-toluamide] content or 20% picaridin [Moskito Guard], appropriate clothing (long-sleeved shirts and long trousers),
- avoiding open spaces from dusk to dawn (the period of the highest activity of insects), especially near water reservoirs (ponds, lakes),
- use of air conditioning in rooms, and screens in windows and over vents.

Following the Centres for Disease Control and Prevention (CDC) and WHO guidelines, in the regions where malaria is endemic, one of the following medications is used as antimalarial chemoprophylaxis (Table 4):

- atovaquon/proguanil - associated with the fewest adverse effects among the presented antimalarials (occasional gastrointestinal disorders, rash, headache),
- doxycycline - numerous adverse effects (nausea, vomiting, oral candidiasis, vaginal candidiasis, hepatotoxicity, sensitivity to sunlight),
- mefloquine - due to neuropsychiatric adverse effects, the product is contraindicated in certain professional groups, e.g. in flight personnel,
- chloroquine - due to the increasing resistance of malaria *Plasmodia* to chloroquine, the medication is effective in the chemoprophylaxis of the disease only in certain regions, e.g. Central America, North Africa, and some countries in the Middle East, which significantly limits its use [17].

Table 4. Recommended antimalarial chemoprophylaxis in countries popular among divers
Tabela 4. Chemioprofilaktyka przeciwmalaryczna zalecana w krajach popularnych wśród nurkujących

Country	Regions of occurrence	Resistance to chloroquine	Chemoprophylaxis recommended
South-East Asia			
Philippines	Rural region under 600 m above sea level, excluding 22 provinces: Aklan, Albay, Benguet, Biliran, Bohol, Camiguin, Capiz, Catanduanes, Cavite, Cebu, Guimaras, Iloilo, Northern Leyte, Southern Leyte, Marinduque, Masbate, Easter Samar, Northern Samar, Western Samar, Siquijor, Sorsogon, and Surigao Del Norte There is no risk of infection in the capital city, Manila, or in other urban areas	Confirmed	Atovaquan/proguanil, doxocycline or mefloquine
Indonesia	Eastern parts of the country (Maluku, Maluku Utara, Nusa Tenggara Timur, Papua and Papua Barat provinces), including Labuan Bajo and Comodo Islands (Nusa Tenggara); rural areas Kalimantan (Borneo), Nusa Tenggara Barat (including Lombok island), Sulawesi, and Sumatra There is a limited risk of infection in rural regions of Java (including Ujung Kulong, Sukalumi and Pangandaran) There is no risk in Jakarta, Ubud and in seaside resorts in Bali, Java, Gili Islands and Thousand Islands (Pulau Seribu)	Confirmed	Atovaquan/proguanil, doxocycline or mefloquine
Malaysia	Rural areas, especially forests in Borneo (Sabah, Sarawak states), and at the peninsula There is no risk of infection in cities and seaside areas (Kuala Lumpur, Georgetown, Penang State, including Penang Island)	Confirmed	Atovaquan/proguanil, doxocycline or mefloquine
Thailand	The provinces along the border with Cambodia, Laos and Myanmar (Burma), as well as Kalasin, Krabi (Plai Phraya district), Nakhon Si Thammarat, Narathiwat, Pattani, Phang Nga (including the city of Phang Nga), Rayong, Sakon Nakhon, Songkhla, Surat Thani and Yala provinces, especially their forests Occasional cases of the diseases in other parts of the Krabi province, in cities and seaside resorts: Bangkok, Chiang Mai, Chiang Rai, Koh Samui, Koh Phangan, and Phuket There is no risk on the islands of the Krabi province (Koh Phi Phi, Koh Yao Noi, Koh Yao Yai, Ko Lanta) or in the Pattaya resort	Confirmed resistance to chloroquine and mefloquine,	**Only** atovaquon/proguanil or doxycycline - the provinces along the border with Cambodia, Laos and Myanmar (Burma), as well as Kalasin, Krabi (Plai Phraya district), Nakhon Si Thammarat, Narathiwat, Pattani, Phang Nga (including the city of Phang Nga), Rayong, Sakon Nakhon, Songkhla, Surat Thani and Yala provinces, Bangkok, Chiang Mai, Chiang Rai, Koh Samui, Koh Phangan, and Phuket - repellents
Indian Ocean			
Andaman Islands (India)	Occasional cases of the disease among the indigenous population	No data	Repellents
Maldives	Does not occur	n/a	n/a
Mauritius	Does not occur	n/a	n/a
Seychelles	Does not occur	n/a	n/a
Pacific Ocean			
Fiji	Does not occur	n/a	n/a
Palau	Does not occur	n/a	n/a
Central America and Caribbean Islands			
Belize	Occasional cases of the disease among the indigenous population Belize City and the islands visited by tourists (Ambergris Caye) are free from malaria transmission	No	Repellents
Cayman Islands	Does not occur	n/a	n/a
Costa Rica	Does not occur	n/a	n/a

Table 4. Recommended antimalarial chemoprophylaxis in countries popular among divers
Tabela 4. Chemioprofilaktyka przeciwmalaryczna zalecana w krajach popularnych wśród nurkujących - cd.

Country	Regions of occurrence	Resistance to chloroquine	Chemoprophylaxis recommended
Mexico	Campeche, Chiapas, Chihuahua, Nayariti Sinaloa states Occasional cases in Durango, Jalisco, Oaxaca, Sonora and Tabasco states, as well as in Othon P. Blanco in the southern Quintana Roo state, along the border with Belize No risk of infection along the Mexican-American border	No	Atovaquon/proguanil, doxycycline, mefloquine or chloroquine - Campeche, Chiapas, Chihuahua, Nayarit and Sinaloa states Durango, Jalisco, Oaxaca, Sonora, Tabasco states and Othon P. Blanco in the southern Quintana Roo state - repellents
Red Sea			
Egypt	Does not occur	n/a	n/a
Mediterranean Sea			
Croatia	Does not occur	n/a	n/a
France	Does not occur	n/a	n/a
Greece	In 2016, cases of infection among the indigenous population were observed. The risk of disease transmission applies to 12 districts: Farkadona, Trikala, Palamas, Tempe, Achaean, Thebes (central Greece), Evrotas, Andravida-Kyllini (Peloponnese), Chalcis (Eubea), Marathon (Attica), Lagada, and Pylaia (Thessaloniki)	No data	Atovaquan/proguanil, doxocycline or mefloquine in the following districts: Farkadona, Trikala, Palamas, Tempe, Achaean, Thebes, Evrotas, Andravida-Kyllini, Chalcis, Marathon, Lagada, and Pylaia
Spain	Does not occur	n/a	n/a
Malta	Does not occur	n/a	n/a
Tunisia	Does not occur	n/a	n/a
Italy	Does not occur	n/a	n/a

Source: www.medycynatropikalna.pl (based on the WHO and CDC 2018 guidelines and recommendations)

Travel first-aid kit

After receiving preventive vaccinations and ensuring appropriate antimalarial chemoprophylaxis before the trip, one needs to prepare a first-aid kit with pharmaceuticals and wound dressing materials, as well as documents such as International Vaccination Certificate, insurance policy, copy of the passport, and passport photographs, in case new visas are necessary during the journey. The first-aid kit should contain:

- medications used daily due to chronic diseases, chemoprophylaxis or contraception, in an amount sufficient for the entire duration of the trip (they should be carried in hand luggage, in the original packaging, in case of border guard control),
- medications used as needed: antidiarrheals, drugs used for respiratory, gastrointestinal, urinary or skin inflammations, analgesics, antipyretics, antiallergic agents; sunscreen; skin disinfectants; eye and ear drops; dressing materials (carried in the main luggage),
- In the case of liquid medications (suspensions, solutions) or cosmetics, airport regulations regarding transportation of liquids should be considered (containers of > 100 ml should be carried in the main luggage, containers up to 100 ml in the hand luggage, in a plastic bag with a closure system).

The contents of the first-aid kit should be individually adjusted to the needs and health requirements of the traveller, as well as the length of the trip planned, climatic conditions, and health risks occurring at the destination country. The medications should be purchased in Poland or in another well-developed country. Analysis of medications produced in developing countries, e.g. in South-East Asia, frequently have a negligible active substance content, resulting in a limited or no therapeutic value compared to the products sold as pharmaceuticals elsewhere. Polish travellers visiting Asiatic or African countries often buy locally produced preparations used in antimalarial chemoprophylaxis, diarrhoea or fever. The products are sold at much lower prices, but have little to do with medicinal products.

Before taking any medication it is necessary to learn about the contraindications for its use, including interactions with other currently used medications, as described in the patient's leaflet. It is recommended to write down the international names of the medications used regularly, in case the first-aid kit is lost, or the medicinal products are used up and their original counterparts need to be purchased [17].

Insurance

Before travelling to places, where recreational or professional diving is planned, it is necessary to purchase an insurance policy, covering medical cost insurance and assistance, in a basic or extended version. The basic coverage has a very limited scope, and multiple

exclusions apply, e.g. the insurance does not cover therapy for tropical diseases or treatment of body injuries caused by extreme sports. **Transportation and repatriation cost insurance is recommended**, and if extreme sports are to be practised, including diving, **emergency services cost insurance** is advisable, as it is not covered by **accident insurance**). Another form of insurance to consider is **baggage insurance**, covering loss, theft or damage of baggage, especially for people who travel with their own diving equipment. An insurance policy for divers should be extended to cover the cost of specialist treatment (e.g. in a hyperbaric chamber), cost of sea rescue, and civil liability (damage to people and things). The insurance cost will also depend on the following: the amateur or professional nature of diving; the use of breathing apparatus up to 30 metres or less than 30 metres; the use of specialist equipment; diver's health status or the presence of chronic diseases.

It should also be emphasised that the insurance company may refuse to pay a claim if the event resulting in health problems took place after the use of alcohol, illegal drugs or other narcotics [17].

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Influence of the "Military Physician" journal on the popularization of haemotherapy and blood donation in Poland, 1920-1939. Part I

Wpływ czasopisma „Lekarz Wojskowy" na rozwój krwiolecznictwa i dawstwa krwi w Polsce w latach 1920-1939. Część I

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Abstract. The years 1914-1940 marked a significant worldwide development in transfusion medicine. On gaining independence, Poland became a place where blood transfusion could be performed and facilities were established where the physiological and pathological processes of such treatments were examined. Attempts were made to organize blood-donation facilities, and the first legal regulations concerning blood donation were introduced. Poles, following the worldwide trend, created blood transfusion devices and undertook research on the practical aspects of banked blood. Articles concerning the history of haemotherapy and the experiences from the First World War were published in "Military Physician", treatment methods and tools were promoted and original transfusion methods were presented. In the 1930s, during the increasing political upheaval in Europe, the requirements for blood service organisation was discussed in "Military Physician" along with the promotion of blood donation. The journal played a significant role in the promotion of blood transfusion know-how among physicians during the twenty-year interwar period in Poland.
Key words: blood, method, physicians, tools, transfusion

Streszczenie. W latach 1914-1940 nastąpił znaczący rozwój światowej transfuzjologii. W Polsce po odzyskaniu niepodległości zaczęto wykonywać zabiegi przetoczeń krwi. Tworzono również placówki zajmujące się badaniem procesów fizjologicznych i patologicznych zachodzących podczas tego zabiegu. Podjęto próby organizacji ośrodków dawstwa krwi. Powstawały pierwsze akty prawne. Polacy, zgodnie z ogólnoświatowym trendem, tworzyli urządzenia do przetoczeń i prowadzili obserwacje nad przydatnością krwi konserwowanej. W „Lekarzu Wojskowym" zamieszczano artykuły poświęcone historii leczenia krwią oraz doświadczeniom z czasu I wojny światowej, propagowano metody oraz narzędzia, przedstawiano autorskie sposoby transfuzji. W latach 30. XX wieku, w czasie narastających w Europie niepokojów politycznych, na łamach „Lekarza Wojskowego" dyskutowano o potrzebie organizacji służby krwi i propagowano krwiodawstwo. Czasopismo „Lekarz Wojskowy" odegrało znaczącą rolę w upowszechnianiu wiedzy o transfuzji krwi wśród medyków w dwudziestoleciu międzywojennym w Polsce.
Słowa kluczowe: krew, transfuzja, metoda, narzędzia, lekarze.

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Introduction

Many discoveries were made during the interwar period, resulting in the establishment of new medical fields. The consequence of this scientific development was the creation of specialist periodicals. In 1920 the first issue of the "Military Physician" journal was published, and quickly gained the recognition and respect of doctors.

The editorial team sought the publication of valuable articles. Articles were submitted by both military and civilian physicians, who were often highly esteemed

authorities in their fields [1]. The articles covered scientific as well as social issues. “Military Physician” was a platform for the exchange of ideas and passionate discussions. One of the popular topics in global medicine in the 1920s and 1930s was blood transfusion, which was neither easy nor commonly used at the time. The procedure was treated similarly to human tissue transplants, and so the consequences and moral responsibility were debated [2]. Blood transfusion was mostly carried out by surgeons. There was no agreement on which of the many methods in use was the most appropriate. Naturally, blood transfusion was a point of interest for military physicians and the history of the procedure is closely associated with military medicine because the key discoveries and organisational guidelines were built around the practical application of blood transfusion during the First World War.

Blood transfusion in early 1900s

As commonly believed, the development of global transfusion medicine began after the discovery of blood types in 1902 by Karl Landsteiner, who was not immediately aware of the importance of his work. However, blood type examination was not practised until much later. Even in the 1920s scepticism regarding the scientific and economic relevance was not uncommon. Transfusions were rarely conducted, and the direct method was common, which involved connecting an artery of the donor with a vein of the recipient via vascular sutures – metal cannulas inserted into the blood vessels. Various devices changing the direction of blood flow were also used. Direct transfusion required numerous assistants and experience in surgery. A significant difficulty was the required presence of the donors. Blood donation via this method carried the risk of health loss, because after the procedure the artery of the donor was ligated and this often led to irreversible disability. It was very difficult to find people willing to risk their own well-being for a stranger.

These methods were complicated and suitable neither in civilian health service nor in a combat environment.

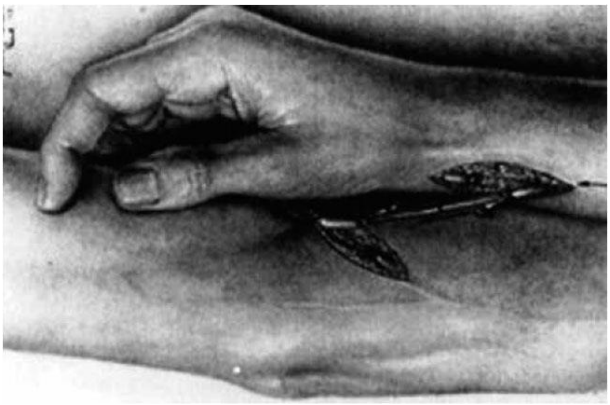

Figure 1. Bernheim's method for the artery-vein connection (Bernheim BM. Bernheim BM. Blood transfusion: Haemorrhage and anaemias. JB Lippincott, Philadelphia 1917:103)
Rycina 1. Metoda Bertrama Bernheima połączenia tętniczo-żylnego (źródło: Blood transfusion: hemorrhage and the anaemias. JB Lippincott, Philadelphia 1917:103)

Blood transfusion during the First World War

During the First World War the following blood transfusion methods were used: direct methods (with vascular sutures, inserting cannulas into the blood vessels of the donor and recipient, more often via syringes redirecting the blood flow [fig. 1]) and indirect transfusions – via syringes (i.e. the Lindemann method) and banked blood. It needs to be noted that methods using syringes changing the blood flow direction (Sokołowski’s, Rutkowski’s, Jube’s) were used in Poland from the First World War until the late 1950s.

Jube’s syringe (fig. 2), 5 or 10 cm^3 in volume, consisted of a piston with a groove, a glass cylinder with two metal pipes on each side connected via rubber hoses, one of which was connected to a needle and the other to a trocar. The required direction of blood flow was achieved by means of the piston, which could be rotated 180 degrees.

A breakthrough in haemotherapy was the use of blood preserved with trisodium citrate. A successful procedure was conducted during the First World War. The first to independently conduct the procedure of transfusion of blood treated with trisodium citrate were Albert Hustin (13 March 1914) and Luis Agote (November 1914). The blood preservation method provided immense capabilities. The development of a method preventing clotting led to the popularisation of transfusion. Preservation provided the possibility of establishing blood banks, which ensured simple and quick access to blood regardless of the presence of a healthy donor.

Figure 2. Jube's syringe (source: www.collection.sciencemuseum.org.uk/objects/co142951/jube-type-blood-transfusion-apparatus-paris-france-1900-1945-blood-transfusion-apparatus [accessed: 10/10/2018])
Rycina 2. Strzykawka Jube (źródło: www.collection.sciencemuseum.org.uk/objects/co142951/jube-type-blood-transfusion-appara-tus-paris-france-1900-1945-blood-transfusion-apparatus [dostęp: 10.10.2018])

The discovery by Ludwik Hirszfeld, a Pole, also contributed to the development of transfusion methodology, as he proved that blood types do not change during a person's lifetime. Today it is an obvious fact, but in the interwar period there was no shortage of reports in global studies on the changes of blood type during the 1st year of a child's life, in adults due to infections, etc.

In conclusion, the establishing of modern blood banks was possible thanks to three discoveries – blood groups, their consistency during a person's lifetime and preservation. The indirect transfusion method combined with blood banks was immediately introduced in the medical services of the deployed armies.

Physicians conducting these ground-breaking transfusions created methods and tools which were then named after them. An example of such a tool was a bottle with trisodium citrate into which the donor donated the blood (Robertson's bottle [fig. 3]). There were various modifications of this invention. Bottles, initially used as containers for blood and sodium citrate, eventually became primitive apparatuses for the collection, preservation, storage and transfusion of blood (fig. 4).

The first guidelines and regulations on the organisation of blood transfusions were established in the United States Armed Forces. During the First World War a special commission was established for the purpose of examining the method of blood transfusion and supervising the process of transfusion. The commission defined the method of banked blood transfusion as valid in the United States Armed Forces. Also developed was an instruction on blood preservation for field hospitals [3].

During the First World War blood type "0" was used in American Armed Forces, which was regarded as universal and appropriate for any recipient. Mixed with glucose and trisodium citrate, it was stored in 500 ml bottles for 26 days and transfused within 4-5 days after donation [4]. It is worth noting that at the time the Rh factor was still unknown. Transfusions were handled by only identifying the blood type of the donor and recipient, not the Rh factor.

Among American and English surgeons a popular method of transfusion involved a device referred to as the Kimpton-Brown tube. Since 1917, the device became mandatory equipment of the medical services of those armies.

These activities were the first attempts to implement blood transfusion (regarded as an experimental procedure at the time) on a larger scale. Blood transfusion was still a rare method, raising many questions and objections. After the war, military doctors and surgeons shared their insights on blood transfusion during scientific meetings. The first papers regarding transfusion and practical observations were presented at the First Interallied Surgical Conference in Paris, which was held while military operations in 1918 were still on-going. The first citations in the literature date from the Fifth World Congress of Surgery in 1920.

The first publications of blood transfusion in the Polish medical press on the basis of articles published in "Military Physician" in the years 1920-1930

In 1920, a single article was published on blood transfusion in "Military Physician" [5]. It has to be noted that it was the first article on the topic published in the Polish medical press after reclaiming independence. Bronisław Szerszyński, a surgeon from the Hospital of Infant Jesus in Warsaw, presented the contemporary

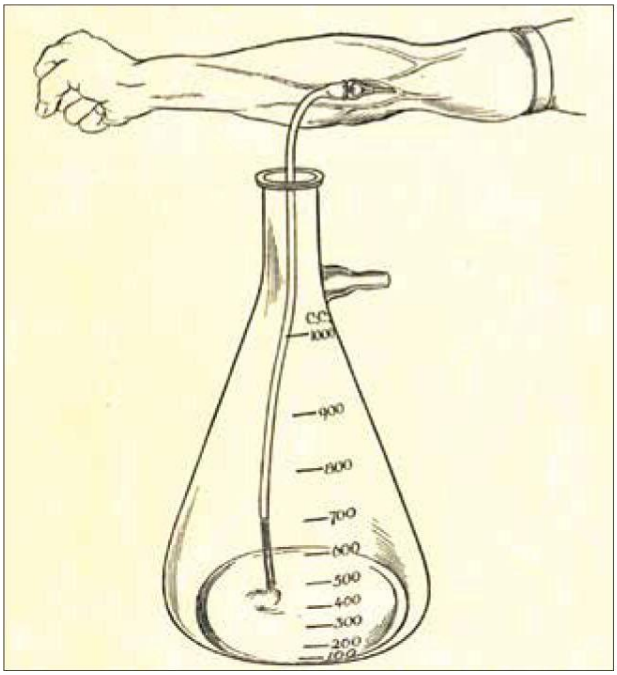

Figure 3. Robertson's bottle (source: Keynes G. Blood Transfusion. London 1922:127)
Rycina 3. Butla Robertsona (źródło: Keynes G. Blood Transfusion. London 1922:127)

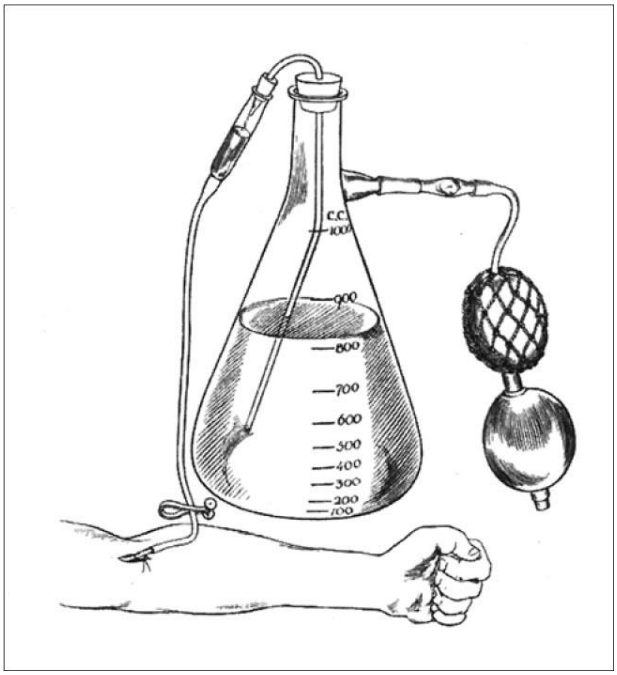

Figure 4. Stansfeld's apparatus (source: Keynes G. Blood Transfusion. London, 1922: 137)
Rycina 4. Aparat Stansfelda (źródło: Keynes G. Blood Transfusion. London 1922:137)

outlooks on blood transfusion [6]. He referred to data originating from international literature and surgical conferences. He provided basic historical facts relevant to transfusion attempts and the methodology of direct transfusion along with its undesirable consequences. He highlighted the significance of blood preservation and its suitability in mass wartime implementation.

This provides a summary of the contemporary knowledge on blood preservation: “The influence of trisodium citrate has not been sufficiently explained. As we know, calcium salts play a key role in clotting, and their sedimentation due to use of, for example, ammonium oxalate which leads to the inhibition of clotting. Trisodium citrate does not sediment nor remove calcium from the blood, but bonds with calcium salts so that the sedimentation of carbonates or oxalates becomes impossible. This provides us with limited insight on why trisodium citrate treated blood does not clot”. Szerszyński noted, however, that on the basis of research and observation, no damage to the red cells was done by the citrate. The article of the experienced surgeon would not be complete without practical guidelines regarding the methods and tools: “Jeanbrand employs a special glass instrument, elongated on the bottom in the shape of a thin beak, which is inserted into an exposed vein. Sterile 10% solution of trisodium citrate is poured into the sterilised instrument (10 cm^3 per 250 cm^3 of blood). The instrument is closed by a lid with a hole into which a hose with a pump used for aspiration during blood extraction. The instrument has to be shaken to mix the blood with the citrate salt solution. The same pump, installed in reverse, can be used to push air into the instrument during transfusion of blood into a vein”. That is the description of a device presented in the first part of the paper: “Kimpton tube” (fig. 5), whose numerous modifications were widely employed for blood transfusion around the world.

He then presented the method of a contemporary percutaneous insertion of a blood vessel, regarded as a bold and innovative procedure: “A slightly simplified technique was adopted in America. Veins are not exposed, the needle is inserted into the vein through skin and the whole instrument comprises a bottle with two hoses: one connected to the needle inside the vein and through the other the doctor sucks out air or blows air inside with his mouth – depending on whether he does the first or the second stage of the procedure. Many surgeons employ even simpler measures: after fixing a rubber band on the limb in order to fill the veins they insert a thick needle, boiled in sodium citrate, and transfers the blood from a container with the citrate, from which the blood is transfused into the vein under the pressure of its own mass via a needle, hose and funnel (or instrument used for Salvarsan pouring). For transfusing smaller amounts of blood one can use a glass 100-200 gram syringe”.

Figure 5. Intravenous administration of blood, with Kimpton's tube, 1916 (source: Bernheim BM. Blood Transfusion, Hemorrhage and the Anaemias. JB Lippincott, Philadelphia 1917:132)

Rycina 5. Podanie dożylne krwi za pomocą tuby Kimptona z 1916 (źródło: Bernheim BM. Blood transfusion: Hemorrhage and the anaemias. JB Lippincott, Philadelphia 1917:132)

Szerszyński listed the contemporary methods of identifying blood types and serological selection of blood donors and recipients. He did not mention the symbols known at the time: A, B, 0, as in the 1920s each scientist who worked on the designation of blood types used their own symbols or adopted a description under non-specific criteria.

The article was written at a time when serums for the identification of blood types were very expensive and available only in some hospitals in the world. In the 1920s, serums were brought to Poland mostly in the luggage of physicians returning from international training sessions.

The designation used to this day (A, B, 0) is attributed to a Pole, Ludwik Hirszfeld and his professor, Emil von Dungern. In 1927, the blood type symbols he proposed were recognised by the Health Committee of the League of Nations as the only applicable system in the world [7]. Types A, B, 0 as we know them today became popular in the 1930s, and the crowning moment was their official recognition by the world's medical society during the 2nd International Congress of Blood Transfusion in Paris in 1937.

Transfusion as an experimental method aroused the curiosity of medical society. Physicians and their personnel took the risk of donating blood, and each transfusion procedure, regardless of the method – direct or indirect – was a scientific event. As time passed and transfusions became commonplace, lists of paid donors were compiled. Medical students eagerly donated blood both out of scientific curiosity and for profit. B. Szerszyński brought up the topic of blood donation in the world: "In larger American Hospitals, people meant to serve as blood donors and medical personnel were first subjected to an examination for that purpose and classified within one of 4 groups".

The author also discussed the topic of research on other sources of blood for transfusions and also mentioned the autologous blood use and methods of obtaining it. After the blood was extravasated into the body cavities (pleura, peritoneum), it was filtered and mixed with trisodium citrate before transfusing it to the patient. It has to be noted that from the 1920s onwards, research on the use of blood from other sources (blood from corpses, placental blood, ill people, bloodletting, therapeutic phlebotomy, extravasation) and recommendations for the procedure were being explored. The author provided data on the use of transfusion in treating various diseases, including infectious diseases: transfusion of blood into the spinal canal of a poliomyelitis patient, in epidemic typhus and influenza. Transfusion of blood was used not only due to anaemia but also in cases of poisoning, shock, chronic kidney disease, or severe anaemia.

The publication of Bolesław Szerszyński constituted a comprehensive discussion on that popular medical topic. In 1920, transfusion with the use of blood preserved with trisodium citrate was a very modern method. The first successful operation had been conducted just 6 years earlier. Publication of an article in the first annual issue of "Military Physician" highlights the ambitions of the editorial committee of creating an innovative world-class medical periodical.

Another propagator of blood transfusion in Poland during the interwar period was a military physician, Franciszek Zalewski. He conducted transfusions by a variety of methods – via Jube syringe and with the use of trisodium citrate treated blood. He was eager to share his practical experiences with "Military Physician". In 1926, he presented a paper in which he described a direct blood transfusion method with the use of Jube and Becard syringes. In 1928, he presented a method of direct blood transfusion that he conducted with the use of commonly available tools. He described the method as simple, elegant and practical.

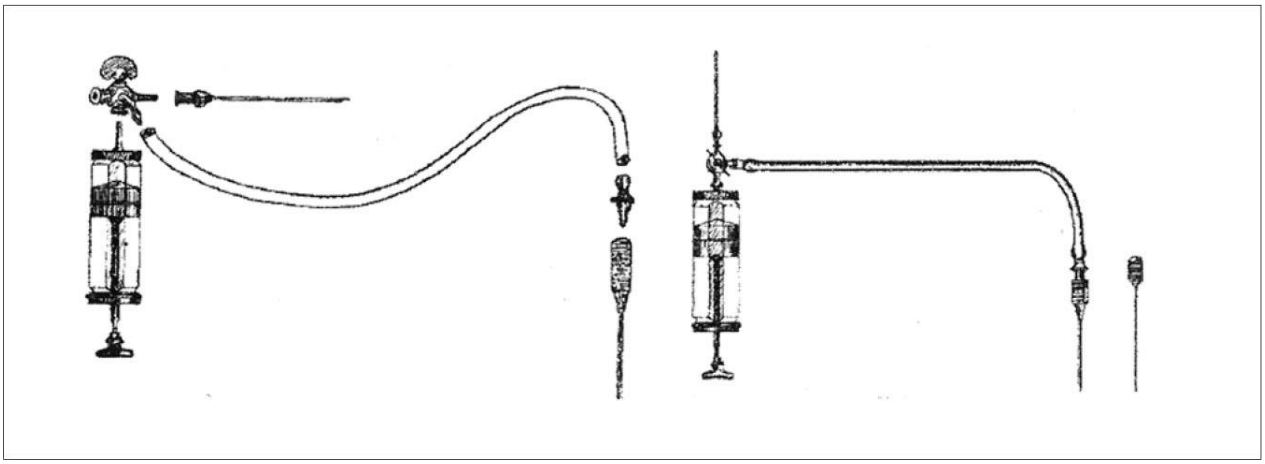

Figure 6. Parts of a Zalewski direct method of blood transfusion set (source: Zalewski F. Najprostszy sposób bezpośredniego przetaczania krwi [The simplest method of direct blood transfusion]. Mil. Phys., 1926; 14 [11]: 4)
Rycina 6. Elementy zestawu do przetoczenia krwi metodą bezpośrednią wg Zalewskiego (źródło: Zalewski F. Najprostszy sposób bezpośredniego przetaczania krwi. Lek Wojsk, 1926; 14 [11]: 4)

Shortages in equipment and medical tools, as well as inadequate funding, forced the physicians to invent creative measures. A set for "Zalewski's transfusion method" (fig. 6) comprised two syringes >10 g in volume, Łogucki valve used for removing fluid from the pleura cavity, a thick needle, 30-40 cm long piece of rubber hose, a thin metal cannula with a trocar and a metal elbow connecting the hose with the metal cannula or a needle for pneumothorax treatment. The direction of blood flow was determined by the valve position. Preparation of the apparatus involved boiling its components, filling it with sterilised paraffin (to prevent clotting – author's note) and then its removal, preparation of a container with a sterile physiological saline, checking the movement of the pistons and preparation of the station for the donor and patient. A trocar was inserted into the recipient's vein and a needle into the donor's vein, the set was filled with physiological saline and individual parts were connected, checking for the presence of air in the apparatus [8].

The donor and recipient were placed next to each other on two tables. The regions of the elbow pits were disinfected with ether or alcohol and covered with a sterile cloth. A trocar with a cannula was inserted into the vein of the recipient, the needle was inserted into the vein of the donor and the rest of the direct transfusion set was connected (fig. 7). Zalewski transferred about 200-300 g of blood at a time. He wrote that this method can be used in the transfusion of blood treated with trisodium citrate directly from a container without the presence of the donor.

Franciszek Zalewski was one of the first medics in the world to employ blood transfusion for the treatment of non-healing skin wounds [9]. His first article on the topic was published in "Military Physician" in 1928. He described in detail the process of healing a large back injury caused by x-ray exposure used for diagnostic and therapeutic purposes employed due to gastric problems at a private doctor's office. The non-healing ulceration spanned between scapulae and coccyx. Zalewski estimated the size of the wound at 28 x 24 cm. At the moment the treatment began the patient was extremely weakened – the 32-year-old man weighed 35 kg. The therapy which involved periodic blood transfusions from "young and strong specimens" was initiated in October 1926. After the first blood transfusion (of 250 cm^3) Zalewski observed an improvement in the man's overall condition and progress in local healing of the ulceration. In April 1927, after the first transfusion, a pulmonary haemorrhage occurred due to tuberculosis. However, the patient's condition improved enough to allow him to get out of bed on his own and his body weight increased to 50 kg. In September 1927, the surface area of the wound spanned 21 x 13 cm but full recovery was not achieved. A skin graft was used. The first one failed. In 1928, another transfusion was made and a skin graft was applied once again – this time with a satisfactory result. Franciszek Zalewski proudly reported: "The patient feels wonderful and is full of vigour, weighs 65.5 kg, mobility around the waist is maintained, he can freely bend over and after almost a three-year-long treatment on our ward he left the hospital as a cured man". It was the first report in the Polish press on the treatment of post-X-ray treatment through blood transfusion. In 1930, the article was translated and published in "Revue de Chirurgie" – a prestigious surgical periodical available internationally [10].

Ten years later, Franciszek Zalewski published another article on the treatment of post-X-ray burns [11]. In the article he provided a critical analysis of the problem, comparing his own observations with reports of other

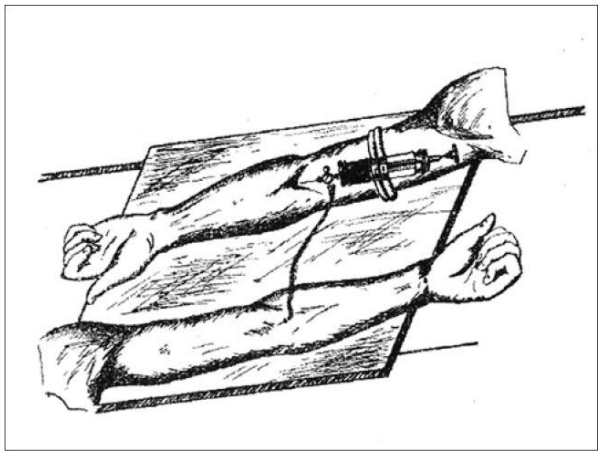

Figure 7. Drawing showing blood transfusion according to the Zalewski method (source: Zalewski F. Najprostszy sposób bezpośredniego przetaczania krwi [The simplest method of direct blood transfusion]. Mil. Phys., 1926; 14 [11]: 4)
Rycina 7. Rysunek przedstawiający transfuzją sposobem Franciszka Zalewskiego (źródło: Zalewski F. Najprostszy sposób bezpośredniego przetaczania krwi. Lek Wojsk, 1926; 14 [11]: 4)

researchers: "Looking through the literature it seems that small scale ulcerations are treatable after a longer period regardless of the method used. However, extensive wounds, especially ones situated in parts of the body with poor perfusion, resist all forms of treatment used previously and the available literature does not contain a single successful recovery in the case of extensive burns treated with previously available methods".

The patient subjected to blood transfusion was a sergeant who had previously been treated by X-ray due to "crotch aphthae". Methods considered standard at the time were initially used: because "the ulceration was small in size and the halfwit patient reluctantly submitted to treatment if I used aseptic dressings (...) the patient did not consent to the suggested transfusion. Meanwhile, with our approval, the patient sought recommendations from other specialists whose guidelines we took into consideration during the treatment". Here it is important to highlight the ethical behaviour of the physicians. The patient did not consent to the proposed treatment, but he was not left without care. He was still treated with the use of available measures that he consented to. The disease progressed and the crotch wound grew larger. After 1.5 years of conservative treatment, blood transfusions were initiated.

The first transfusion by Zalewski was done in April 1933. Due to the improvement in the wound's state the procedure was repeated, transfusing blood seven times within 4 months. The healing process progressed slowly. A swab from the ulceration was taken, a "chain-like" bacterium was grown (most likely streptococcus or staphylococcus, at the time microbial cultures and bacteriological tests were a very modern procedure – author's note); it was eliminated and a skin graft was used, which failed, according to Zalewski. However, by 1935 the crotch wound was healed.

The procedure of Franciszek Zalewski was innovative and modern. He was no doubt one of the pioneers of Polish transfusion medicine, although unfortunately his scientific work was interrupted by the outbreak of the Second World War.

Summary

One of Poland's first medical periodicals established after reclaiming independence was "Military Physician". Popular among Polish physicians, it formed opinions and promoted medical knowledge.

In the 1920s, blood transfusion was a rarely used method. Articles submitted to "Military Physician", which contained medical knowledge regarding blood transfusion encouraged physicians to employ transfusion and promoted not only the method but also blood donation. Theoretical papers and reports on executed procedures were met with high interest from the readers.

In the following years transfusion medicine saw enormous progress, which made this formerly rarely used procedure commonplace in medical practice. The following stages of global transfusion medicine and the role of Poles in the process will be presented in the second part of the article.

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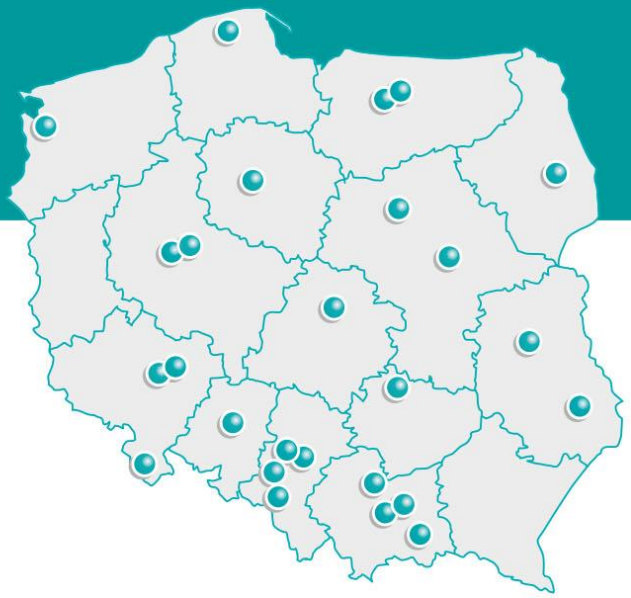

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