Drug utilisation trends in a physical rehabilitation hospital

Trend primene lekova u bolnici za fizikalnu medicinu i rehabilitaciju

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Abstract

Background/Aim. Drug utilisation monitoring could identify drug-related problems and hence improve the awareness of irrational drug use. The objective of this study was to analyse the drug utilisation patterns in a rehabilitation hospital over the period 2011–2016. Methods. The Anatomic Therapeutic Chemical classification/Defined Daily Dose (ATC/DDD) methodology was used to monitor the drug utilisation expressed as a number of DDD per 100 patient-days (HPD). The values of DDDs were obtained from the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology. Utilisation trends were analysed by means of the Compound Aggregate Growth Rate (CAGR), which is defined as an average annual change rate of some value during the period of interest. Results. The number of patient-days increased during the six years period; the CAGR being 1.8% annually. At the same time, the total number of dispensed DDDs as well as the number of DDD/HPD decreased with the CAGR of -2.0% and -3.7% respectively. The average drug cost per patient-day varied from BAM 1.38 in 2013 to 0.95 in 2016; the CAGR being -1.8%. The most utilised drugs belonged to the ATC groups C, A, B, M and N and they contributed to an average of 77% of all drugs used each year. On the top of the list of most utilised drugs were: hydroxocobalamin, thioctic acid, enalapril, diclofenac, amlodipine, acetylsalicylic acid, pantoprazole, paracetamol and bromazepam. Conclusions. The overall drug utilisation in the hospital was modest and almost equal in 2016 compared to 2011. Besides the leading consumption of vitamin B12 and thioctic acid, this study points out some interesting prescribing patterns, such as predominant use of diclofenac over ibuprofen, and overuse of proton pump inhibitors. There is a need for educational interventions among physicians in order to improve their prescribing practice.

Key words: hospitals; physical and rehabilitation medicine; drug therapy; drug utilisation.

Rezultati. Broj bolničkih dana rastao je tokom šestogodišnjeg perioda (CAGR 1.8% godišnje). Ukupan broj DDD lekova izdatih na odeljenja i broj DDD/100 bolničkih dana pokazali su pad (CAGR -2.0% i -3.7%, respektivno). Dnevna potrošnja lekova je finansijski varirala od 1,38 KM u 2013. do 0,95 KM u 2016. godini, sa CAGR -1,8%. Najviše su korišćeni lekovi iz ATC grupa C, A, B, M i N koji su zajedno činili u proseku 77% godišnje potrošnje lekova tokom posmatranog perioda. Najzastupljeniji lekovi po potrošnji bili su hidroksikobalamin, alfa-lipoina, enalapril, diklofenak, amlopidin, acetylsalicylic acid, pantoprazole, paracetamol i bromazepam. Zaključak. Potrošnja lekova u našoj ustanovi bila je skromna i gotovo bez promena 2016. godine u odnosu na 2011. godinu. Osim prominentne potrošnje vitamina B12 i alfa-lipoićke kiseline, usta-
novljen su i neka odstupanja od racionalnog propisivanja lekova poput prekomerne potrošbe diklofenaka u odnosu na ibuprofen, te značajna potrošnja inhibitora protonski pumpa. Potrebne su ciljane i kontinuirane edukacije radi unaprjeđenja prakse propisivanja lekova.

**Introduction**

Therapeutic practice is primarily based on evidence provided by pre-marketing clinical trials, which could be later transferred into therapeutic guidelines and clinical protocols. However, complementary post-marketing data based on drug utilisation analyses also contribute to improvement of drug therapy. The World Health Organisation (WHO) defined the drug utilisation research (DUR) as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”.

Drug utilisation monitoring could identify drug-related problems and hence improve the awareness of irrational drug use. Data on drug utilisation in correlation with morbidity data, clinical and economic health care outcomes and quality of care could be of special value. It could also provide a feedback to physicians and the recommendations for health professionals to improve the prescribing practice. Drug utilisation could have varied patterns among the different health institutions as well as among the different countries. In order to compare and discuss the differences and structure of drug utilisation, it has to be expressed in the internationally accepted units and daily doses (DDD) has to be defined. The DDD per 1,000 inhabitants per day (DDD/TID) is often used to derive a rough estimate of prevalence of drug use in the population being studied. Until recently, we have published several papers related to the drug utilisation analyses.

When the hospital drug use is considered, the drug consumption figures should preferably be presented as numbers of DDD per 100 hospital bed-days (DDD/HBD). Despite advances in the DUR area, there is a paucity of information on hospital drug utilisation in our country. In general, studies on the inpatients’ drug use are often incomplete, mainly because it is difficult to obtain precise, accurate and structured data necessary for this type of analysis.

The aim of this study was to determine the drug utilisation trends at the biggest rehabilitation hospital in The Republic of Srpska (Bosnia & Herzegovina). Moreover, this research intends to identify the deviations of prescribing behaviour from the recommendations and guidelines as well as to propose measures for practical improvement and rationalisation of drug use.

**Methods**

This was a retrospective, six-year (2011-2016) drug utilisation analysis performed at the physical rehabilitation hospital (Institute of Physical Medicine and Rehabilitation “Dr Miroslav Zotović”, Banja Luka). With a total capacity of 576 beds, this is the largest hospital of such kind in the country, specialised in physical medicine and rehabilitation, orthopaedic surgery and baromedicine. This study included only drugs dispensed by the hospital pharmacy department to the adult rehabilitation wards with total of 480 beds. The paediatric rehabilitation unit as well as orthopaedic surgery ward were excluded from the study due to the limitations of ATC/DDD methodology and different patterns of drug use, respectively.

The data related to the drug utilisation and hospital occupancy rate were obtained from the hospital information system, and the statistical analysis was performed by the hospital pharmacy department. All drugs were identified by the generic names and coded according to the Anatomical Therapeutic Chemical (ATC) classification. For this purpose, the data on ATC codes and the DDDs for dispensed drugs were taken from the ATC/DDD Index, 2016. DDD was established for 224 out of total of 286 different dispensed drugs. Drugs with no declared DDD (for example infusions or anaesthetics) were excluded from the analysis.

The annual number of patient-days was obtained as a sum of inpatient-days and outpatient-days for a specific year. We preferred a term “patient-day” instead of “bed-day” because both inpatient and outpatient data were included in our results. Other authors have also proposed the “patient-day” as a denominator. For the analysis of the total drug costs, the average drug costs per patient-day and number of different International Nonproprietary Names (INNs) were included.

The data on drug utilisation (for drugs with the DDD) were expressed as a number of DDDs per 100 patient-days (DDD/HPD) as follows:

\[
\text{DDD/HPD} = \frac{\text{total number of units x unit strength}}{\text{DDD x number of patient days}} \times 100
\]

Utilisation trends were analysed by the Compound Aggregate Growth Rate (CAGR). CAGR is defined as an average annual change rate of some value during the period of interest, according to the following formula:

\[
\text{CAGR} = \left( \frac{\text{value in last year}}{\text{value in first year}} \right)^{\frac{1}{\text{number of years}}} - 1
\]

The drug utilisation data in DDD/HPD were processed at the first and the second ATC level. The most utilised drugs, at the level of INN, were analysed in details. All DDD-designated drugs were also analysed according to their administration route.

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Ljubojević G, et al. Vojnosanit Pregl 2019; 76(12): 1261–1267.
Results

The total number of 1,104,552 patient-days in the six-year period comprised of 1,034,577 inpatient and 69,965 outpatient days, with an average of 184,092 patient-days/year. The annual number of patient-days increased during the six-year period; the difference between 2011 and 2016 being 16,051 patient-days, with CAGR of 1.8% annually. At the same time, the total number of dispensed DDDS as well as the number of DDD/HPD decreased with CAGR of -2.0%, and -3.7%, respectively (Table 1).

The total cost of dispensed drugs during the six-year period was 1,232,033 BAM. Although the annual cost of all drugs showed some fluctuations, there was no significant difference between the first and the last year. The cost of drugs with the established DDD in 2016 was lower than in all other years, with CAGR being -1.0%, while the annual cost of drugs with no DDD significantly increased over the years, and CAGR was 4.5%. The cost of drugs per DDD showed no significant difference; the CAGR being 0.3%. The average drug cost per patient-day varied from BAM 1.04 in 2013, to 0.95 in 2016; the CAGR being -1.8% (Table 2).

The drugs that belonged to the groups A, B and C were the most frequently used medicines during the whole study period. They contributed to an average of 77% (range 72%–88%) of all drugs used each year. During the first four years (2011–2014), the cardiovascular drugs (group C) were the most frequently used. However, in 2015 and 2016, the most utilised ones were the drugs acting on blood (group B) and the drugs acting on the alimentary tract and metabolism (group A), respectively. The drugs acting on the nervous system (group N) were in the fourth place representing 7.42%–9.55% of all medicines used (Table 3). According to the administration route, oral formulations were dominant (62.9%).

On the list of top 20 most utilised drugs, the group A was represented by 7 drugs: thioctic acid (the second most utilised drug), pantoprazole, ranitidine, omeprazole, bisacodyl, lactic acid-producing organisms and metformin. The use of proton pump inhibitors (PPIs), particularly pantoprazole, significantly increased over the years; from 0.07 DDD/HPD in 2011 to 3.44 DDD/HPD in 2016; the CAGR being 119.3%. The use of omeprazole was very stable over the years with an average of 2.25 DDD/HPD. At the same time, the use of ranitidine significantly decreased from 4.90 and 5.31 DDD/HPD in 2011 and 2012, respectively, to 2.18 DDD/HPD in 2016 (the CAGR being -15%; Table 4).

The most utilised drug in the group B was hydroxocobalamin (vitamin B12) with an average of 23.88 DDD/HPD, followed by acetyl salicylic acid (ASA) and clopidogrel. The use of ASA in 2016 (3.58 DDD/HPD) was significantly lower than in 2011 (8.14 DDD/HPD), or in 2012 (9.34 DDD/HPD); the CAGR being -15.2% (Table 4). Other drugs of the group B used in hospital were rivaroxaban, enoxaparin, dalteparin, but their use was negligible.

The group C was represented by enalapril, which was the third most utilised drug in the hospital (average DDD/HPD was 14.32), followed by amiodipine (in the fifth place). The use of amiodipine had a constant increase from 2011 to 2013 (6.04, 7.03 and 10.01 DDD/HPD, respectively), but it significantly decreased in the following three years (6.44, 5.02 and 3.87 DDD/HPD in 2014, 2015 and 2016, respectively; Table 4). Furosemide and hydrochlorothiazide were also present on the top 20 list.

Table 1

| Year          | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | CAGR[ %] |
|---------------|------|------|------|------|------|------|----------|
| Patient-days  | 172,148 | 175,599 | 185,977 | 193,358 | 189,271 | 188,199 | 1.8      |
| Total DDD     | 237,354 | 292,305 | 372,426 | 242,785 | 223,160 | 214,432 | -2.0     |
| DDD/HPD       | 137.88 | 166.46 | 200.25 | 125.56 | 117.90 | 113.94 | -3.7     |

DDD-defined daily dose; HPD – 100 patient days; CAGR – Compound Aggregate Growth Rate.

Table 2

| Year          | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | CAGR[ %] |
|---------------|------|------|------|------|------|------|----------|
| Total drug cost (BAM) | 178.682 | 216.677 | 256.495 | 216.363 | 185.880 | 177.937 | -0.1     |
| Cost of drugs with established DDD (BAM) | 152.899 | 180.116 | 213.360 | 183.905 | 158.619 | 145.752 | -1.0     |
| Cost of drugs per DDD (BAM) | 0.64 | 0.62 | 0.57 | 0.76 | 0.71 | 0.68 | 0.3      |
| Cost of drugs with no DDD (BAM) | 25.783 | 36.561 | 43.135 | 32.457 | 27.261 | 32.184 | 4.5      |
| Cost of drugs with DDD/Total drug cost (%) | 85.6 | 83.1 | 83.2 | 85.0 | 85.3 | 81.9 | -0.9     |
| Average drug cost/patient-day (BAM) | 1.04 | 1.23 | 1.38 | 1.12 | 0.98 | 0.95 | -1.8     |

*1 BAM = 0.5113 EUR; DDD – defined daily dose; CAGR – Compound Aggregate Growth Rate.

Ljubojević G, et al. Vojnosanit Pregl 2019; 76(12): 1261–1267.
Diclofenac (group M) was in the fourth place of the top 20 list of the most utilised drugs in the hospital. However, its use significantly decreased over the years; from 9.82 DDD/HPD in 2011 to 4.00 DDD/HPD in 2016; the CAGR being -16.4%. Other nonsteroidal anti-inflammatory drugs (NSAIDs) used in the hospital were ibuprofen, meloxicam, ketoprofen and dexketoprofen, but their use was significantly lower than the use of diclofenac (Table 4).

The use of paracetamol (group N) was very constant over the time with an average of 3.29 DDD/HPD. On the other hand, the use of tramadol was very low (on an average 0.03 DDD/HPD) with a mild decreasing trend (CAGR -
rehabilitation is usually a time-demanding process, with the consequently to the increased drug consumption. However, increased number of patients treated in hospital and hospital pharmacy personnel is strictly obliged to dispense the generic drugs only, which is a proven indicator of trends as the drugs with the DD D. As a matter of fact, the use of new, more expensive drugs, but may also be a consequence of the increased drug prices. To a certain cost per DDD. This could be partly because of the increased utilised DDDs decreased, resulting in a bit higher average to BAM 0.95 in 2016. On the other hand, the total number of patient-days showed slight, but constant increase. This resulted in the patients with the low back pain and diabetic neuropathy.

Discussion

The results of this study showed that there was a constant increase in the total drug utilisation from 2011 to 2013, followed by a significant decrease until the end of 2016. The same trend was observed in the financial values, as well, while at the same time the number of patient-days showed slight, but constant increase. This resulted in the decreased drug cost per patient-day from BAM 1.04 in 2011 to BAM 0.95 in 2016. On the other hand, the total number of utilised DDDs decreased, resulting in a bit higher average cost per DDD. This could be partly because of the increased use of new, more expensive drugs, but may also be a consequence of the increased drug prices. To a certain number of drugs, the DDD was not assigned, so they were analysed in the financial context only. Nevertheless, it can be concluded that the utilisation of these drugs follows similar trends as the drugs with the DDD. As a matter of fact, the hospital pharmacy personnel is strictly obliged to dispense the generic drugs only, which is a proven indicator of reduced drug costs, according to the WHO. Compared to some other studies, the overall drug utilisation in this study was quite low. There could be several reasons for that. First of all, the study was performed at rehabilitation hospital where the physical procedures are dominant and pharmacological treatment was used only as a complementary one. Secondly, purchasing and dispensing the drugs were based on the principles of rational prescribing, according to the hospital formularies with generic prescribing and careful management of available resources, including the transparent public drug procurement system. Furthermore, before coming to rehabilitation hospital, most of the patients were treated in some other healthcare facilities and they would usually bring their own medication upon admission to hospital.

An increased occupancy rate, which was related to the shorter hospital length of stay in recent years has led to the increased number of patients treated in hospital and consequently to the increased drug consumption. However, rehabilitation is usually a time-demanding process, with the rare acute medical conditions, and thus with a stable drug consumption. Domination of oral dosage forms is consistent with the morbidity patterns, and only a minority of patients had a serious medical reason for parenteral therapy. The parenteral drug administration was a choice when oral forms were not available, or when a rapid onset of drug action was needed. The significant differences between the DDD and the actual dose for some drugs had a strong impact on the study results.

The most prescribed drugs were from the ATC groups B, A and C. The group B was prominent mainly because of the widespread use of vitamin B12. Although vitamin B12 is known to be important for nerve function, there is no consensus about the optimal dose of vitamin B12 supplementation. It is obvious that prescribing of a very high dose of vitamin B12 (2.5 mg versus 20 µg according to the DDD for hypovitaminosis) in off-label indication (e.g., diabetic neuropathy and radiculopathy) led vitamin B12 to the first position. This finding is also in correlation with a study of Janković et al. Other authors reported the administration of ten-fold dose of vitamin B12 in comparison with the recommended dietary allowance as oral, but not as parenteral form. The rationale for this off-label prescribing are the convincing results of some randomised clinical trials that showed an antinociceptive potential of vitamin B12 in the patients with the low back pain and diabetic neuropathy.

Thioctic acid was the most frequently used drug in the group A. A daily dose of this drug for diabetic neuropathy (600 mg) is three-fold the DDD, which might be misleading because actually 4.6 of 100 patients were receiving this drug despite of the consumption de facto of 13.73 DDD/HPD. Although it is known that aspirin decreases the incidence and the mortality of vascular disease and cancer, the utilisation of the low-dose aspirin decreased over recent years. It is possible that its wider prescription and use are seriously impeded by physicians’ concerns of gastrointestinal bleeding.

The increased trend of PPIs utilisation (omeprazole and pantoprazole) was complementary to the decreased use of ranitidine. This could be due to recommendations for extensive use of these drugs for gastrointestinal protection in the patients on the long-term NSAID treatment. A relevant literature survey also suggested that PPIs produce more sustained gastric acid suppression, as compared to H2-blockers and promote the ulcer healing despite the continued NSAID use. However, it was reported that the long term use of PPIs is associated with a wide range of adverse effects, including increased risk of infection, reduced intestinal absorption of iron (anaemia) and calcium (bone fractures), and more recently the kidney damage and dementia. Therefore, the additional efforts are needed to reconsider the appropriate use of PPIs.

As expected, NSAID diclofenac and analgesic drug paracetamol were within the top 10 drugs at the positions 4 and 8, respectively. Diclofenac is a widely used medicine for relieving pain and inflammation, particularly in painful conditions such as arthritis. Despite of some decline, the

Ljubojević G, et al. Vojnosanit Pregl 2019; 76(12): 1261–1267.
Sertraline is one of the reasons for a significant sertraline use, in antidepressants other than sertraline was obvious, despite the analgesics of choice for the treatment of neuropathic pain. Tricyclic antidepressants, selective serotonin-norepinephrine reuptake inhibitors and anti-convulsants as adjuvant fact that the current treatme nt recommendations suggest oxygen therapy. It is known that HBOT is followed by otalgia, ear fullness, hearing loss, and tinnitus as the most prevalent symptoms. Nevertheless, it seems that the topical nasal decongestants may not be effective in preventing the middle ear barotrauma during the hyperbaric oxygen therapy.

Overall antibiotic utilisation was relatively stable with a small increase in 2013. The hospital has developed its own antibiotics guidelines, the Guidelines for the Prevention and Treatment of Urinary Tract Infection, as well as the Guidelines for Chronic Wound Infection. Moreover, the local Drug and Therapeutic Committee is obliged to periodically report on the utilisation of antibiotics in the hospital. Despite the hospital guidelines for the antimicrobial therapy, doctors are very prone to prescribe the broad-spectrum antibiotics for empirical treatment of bacterial infections. Hence, ciprofloxacin (both oral and parenteral) was found on the list of top 20 drugs. In general, the hospital monitoring of antimicrobial utilisation is important in order to establish the relationship between their use and the occurrence of resistance. Monitoring also reveals trends in prescribing and allows comparisons to be made among different hospitals.

The present study has several limitations. The main one is that the data on drug utilisation were available only for drugs dispensed from the hospital pharmacy department; hence personal patient’s drugs were not included. Therefore, it remains unknown whether the total drug consumption follows the observed trends. Also, the data are collective and not analysed according to diagnoses. Consequently, additional studies are needed to determine the prescribing patterns and drug utilisation for major conditions treated in the hospital.

Conclusion

It could be concluded that the general pattern of drug utilisation is consistent with the most common conditions treated in the hospital. Additionally, this study points out a few deviations in prescribing habits and these points could be a target for the future educational activities. Our results are not surprising as there is a lot of space for harmonisation of the prescribing practice with the current recommendations and clinical guidelines.

References

1. Strom BL. Pharmacoepidemiology. 4th ed. Chichester, UK: John Wiley and Sons; 2006.
2. World Health Organization. Introduction to Drug Utilization Research. Oslo, 2003. Available from: http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf. [accessed 2017 March 27].
3. Zutapa A, Vijayakumar S, Jayaraman B, Patel D, Narayan M, Vijayakumar K, et al. An informatics approach to assess pediatric pharmacotherapy: design and implementation of a drug utilization system. J Clin Pharmacol 2007; 47(9): 1172–80.
4. Wettermark B, Elseviers M, Almarsdottir AB, Andersen M, Benko R, Bennie M, et al. Introduction to drug utilization research. In: Elseviers M, Wettermark B, Almarsdottir AB, Andersen M, editors. Drug Utilization Research: Methods and Applications. Chichester: John Wiley & Sons; 2016. p. 1–12.
5. Jhaever BN, Patel TK, Baruahya MJ, Tripathi CB. Drug utilization pattern and pharmacoeconomic analysis in geriatric medical inpatients of a tertiary care hospital of India. J Pharmacol Pharmacother 2014; 5(1): 15–20.
6. Chatterjee S, Mandal A, Lyne N, Mukherjee S, Singh AK. Drug utilisation study in a neonatology unit of a tertiary care hospital in eastern India. Pharmacoeplimology Drug Saf 2007; 16(10): 1141–5.
7. Topić M, Cepić R, Clarence A, Bonati M. Methods in pharmacoepidemiology: a review of statistical analyses and data reporting in pediatric drug utilization studies. Eur J Clin Pharmacol 2013; 69(3): 599–604.
8. Janković S, Đukanović Ž, Drug utilization trends in Clinical hospital centre 'Kragujevac' from 1997-1999. Ind J Pharmacol 2000; 33: 29–36.
9. Marčović-Peković V, Škreb R. Long-term drug use and polypharmacy among the elderly population in the Republic of Srpska; Bosnia and Herzegovina. Vojnosanit Pregl 2016; 73(5): 435–41.
10. Marković-Peković V, Škreb R, Petrović A, Vlaković-Palčevski V, Smok J, Bennie M, et al. Polypharmacy among the elderly in the Republic of Srpska: extent and implications for the future. Expert Rev Pharmacoecon Outcomes Res 2016; 16(5): 609–18.
11. Marković-Peković V, Škreb R, Godman B, Gustedson LL. Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions. Expert Rev Pharmacoecon Outcomes Res 2012; 12(5): 661–71.
12. Marković-Peković V, Stjanić-Jovanović S, Škrbić R. Outpatient utilization of drugs acting on nervous system: a study from the Republic of Srpska, Bosnia & Herzegovina. Eur J Clin Pharmacol 2010; 66(2): 177–86.

13. Marković-Peković V, Stjanić-Jovanović S, Škrbić R. Utilisation of cardiovascular medications in Serbia, Bosnia and Herzegovina, 5 years study. Pharmacoepidemiol Drug Saf 2009; 18(4): 320–6.

14. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2017. Oslo: 2016. 20th ed. Available from: https://www.whocc.no/ fi-learchive/publications/2017_guidelines_web.pdf. [accessed 2017 March 28].

15. Škrbić R, Babić-Durdić D, Stjanić-Jovanović S, Stojanović N, Nežić L. The role of drug donations on hospital use of antibiotics during the war and postwar period. Int J Risk Safety Med 2001; 14(1–2): 31–40.

16. Compound Aggregate Growth Rate - CAGR. Available from: http://www.investopedia.com/terms/c/cagr.asp [accessed 2017 July 27].

17. Rajaratnam K, Viswanath M, Ramasamy AD, Kamath SD, Sukritiha S, Hashbota A, et al. Evaluation of WHO prescribing indicators among orthopaedic inpatients at tertiary care hospital. J Chem Pharm Res 2014; 6(8): 278–80.

18. Godman B, Wittnermark B, van Wuerkom M, Freyerman J, Alhazr Madaen S, Berg C, et al. Multiple policies to enhance prescribing of clofibrate in France, with a particular focus on demand-side measures: findings and future implications. Front Pharmacol 2014; 5: 106.

19. Goldberg H, Mithiell MA, Names CP, Goldberg SW, Buchman L, Mezzini SG, et al. A double-blind, randomized, comparative study of the use of a combination of uridine triphosphate trisodium, cytidine monophosphate disodium, and hydrocortisone in patients presenting with compressive neuralgias. J Pain Res 2017; 10: 397–404.

20. Smelt HJM, Pouwels S, Smulders JF. Treatment of otological complications associated with hyperbaric oxygen therapy. Eur Arch Otorhinolaryngol 2016; 273(9): 2487–93.

21. Yamanoto Y, Noguchi Y, Enomoto M, Yagishita K, Kitamura K. Barotrauma after Hyperbaric Oxygen Therapy – Insights on Pathophysiology. Int Arch Otorhinolaryngol 2014; 18(2): 204–9.

22. Capes JP, Tomaszewski CM. Hyperbaric Oxygen Therapy – Insights on Pathophysiology. Int Arch Otorhinolaryngol 2014; 18(2): 204–9.

23. Ljubojević G, et al. Vojnosanitetski Pregled 2019; 76(12): 1261–1267.