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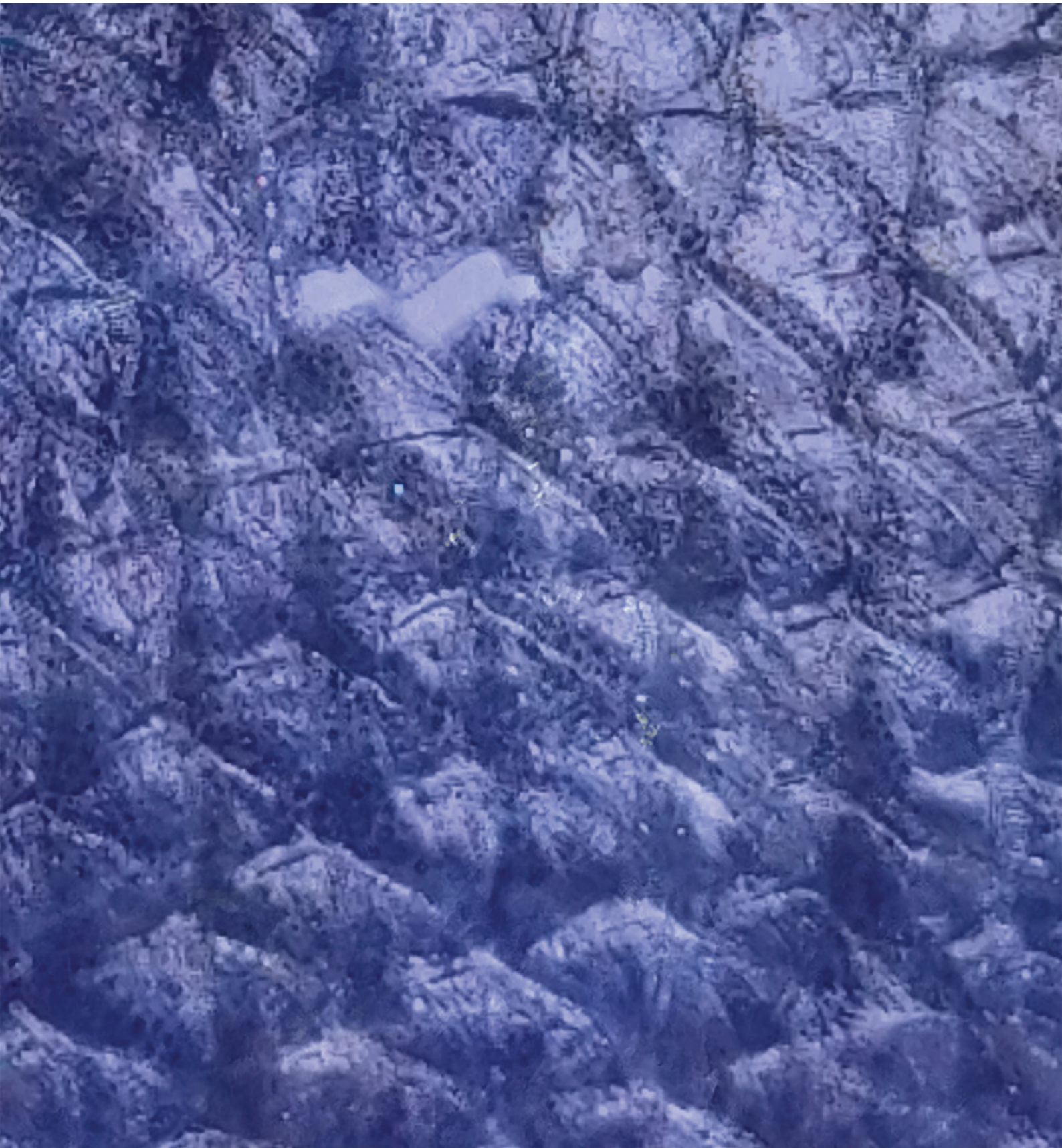

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Financial aspects of rationalisation of consumptions of medicaments from essential list in Sarajevo canton

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Abstract

Introduction: Health is a basic human right, and the right for health care, which includes the availability of essential medicaments and that, is a basic precondition for implementation of that right.

Material and methods: The paper presents an overview of medicaments consumption for the period 2011-2016, with reference to 2017. The consumption of medicaments for the mentioned period from the essential list was analyzed, as well as other consumption that is in the structure of costs for medicines in the budget of the Health Insurance Institute of Sarajevo Canton.

Results: The analysis showed that out of the total number of insured persons, 60% of them took prescription drugs, while the remaining 40% did not use health services or they did not took drugs.

Discussion: It was shown how the measures were taken to rationalize the consumption of medicines, and that the key role was played by the tools in the integrated informational system that enabled the evaluation and control of the consumption of medicines. Savings on medicines were recorded, but not to the detriment of the insured of the Sarajevo Canton. In this system, the patient received exactly the amount of medicine they needed without creating unnecessary "home pharmacies".

Conclusion: The drug market is highly regulated, because health has the status of a public good. The usual laws of supply and demand do not apply in the pharmaceutical market and do not depend on market prices. The demand for medicines is influenced by demographic changes in the structure of the population, chronic diseases, the introduction of new innovative medicines, and the supply of medicines is carried out according to the laws regulating the market of medicines.

Key words: esential list of medicaments, market share, rationalisation of medicaments consumption.

Introduction

The health sector is generally divided into public and private, both in Bosnia and Herzegovina and in Sarajevo Canton. Regarding the pharmacy activity in the Sarajevo Canton, there are 50 public and 124 private pharmacies, which provide pharmaceutical services to patients and service users. Medicines that belong to the Rx category (medicines that are issued only on a doctor's prescription), and which are on the essential list of the Sarajevo Canton, can be sold in the same way in both the public and private sectors. Throughout history, only public pharmacies have had this privilege, after which a network of pharmacies was created where only a couple of private pharmacies managed to enter the network and obtain the status of a "contract pharmacy". Thanks to the Council of Competition, all pharmacies that meet the conditions prescribed by law (1) and regulations (2) can receive the status of "*contract pharmacy"*.

Each "contracted pharmacy" has a contract with the Health Insurance Institute of Sarajevo Canton, which defines the price of a pharmaceutical service for dispensing prescription drugs. The price per prescription has been reduced from 1.90 to 1.65 BAM with VAT by the Decision of the Management Board of the Health Insurance Institute of the Sarajevo Canton since June 2016.

As the pharmaceutical market of medicines is specific, so is the marketing of pharmaceutical prod-

ucts, because medicines and medical devices that have special purposes for maintaining health, as well as for disease prevention, must be strictly regulated and be under constant supervision of professionals.

The pharmaceutical market is very complex and the following actors participate in it: (3)

1. Patients who pay directly to health care providers, i.e. health needs and who also pay fees and premiums to the state or insurance fund,

2. Service providers - doctors, pharmacists who send invoices to the fund and which the fund pays (refunds),

3. An insurance fund that pays health care providers and that covers patient insurance.

All three actors are controlled and regulated by the ministry and the government with their legal regulations.

From year to year, there is an evident increase in the cost of medicines from the essential list in the Sarajevo Canton, despite the fact that every year there is a drop in individual drug prices. The importance of the problem is also shown by the share of costs for medicines in the Sarajevo Canton in the total expenditures, which in the previous period ranged from 19.7% in 2011 to 23.8% in 2016. (4) All this significantly burdened the budget of the Health Insurance Institute of Sarajevo Canton, so it is very important to analyze and monitor the consumption of drugs, the causes of increased consumption, all with the aim of greater rationalization of consumption and taking appropriate measures and activities to manage and control drug consumption.

In the pharmaceutical industry, it is necessary to use an informational system to monitor the prescribing medicaments by doctors. (5)

The essential list of medicines is being revised every year and set with the Federal List of Medicines, i.e. the Commission for Medicines performs a revision and sets the list with the Federal one. Sarajevo Canton is known for regularly updating and coordinating the list with the legal framework. In Sarajevo Canton, in addition to List A, which is binding for all cantons with 100% participation of the Institute, there is also List B, which is optional with the participation of the Health Insurance Institute of 25%, 50% and 75%. The biggest change of the essential list in this period occurred in the second part of 2016 when the new Decision on positive, hospital and main list of medicines of Sarajevo Canton (6) came into force with precisely defined indication areas and professional doctrinal guidelines, and time availability of therapy (VDT).

The introduced guidelines and restrictions resulted in savings as well as more rational consumption of medicines in the second half of 2016.

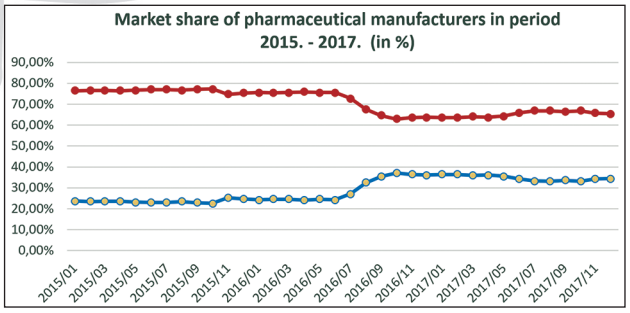
By innovating the binding guidelines "e Guidelines" for drugs use, it had been established the right of the insured person of the Institute for which disease, for how long, in what time interval and under what circumstances can use certain drugs at the expense of the Institute, thus creating the preconditions that determined rules in specific number of guidelines, can implement and control exclusively through an integrated informational system.

Material and methods

The paper presents an overview of drug consumption for the period 2011-2016, with a review of 2017. The consumption of medicines for the mentioned period from the essential list was analyzed, as well as other consumption that is in the structure of costs for medicines in the budget of the Health Insurance Institute of Sarajevo Canton.

The results

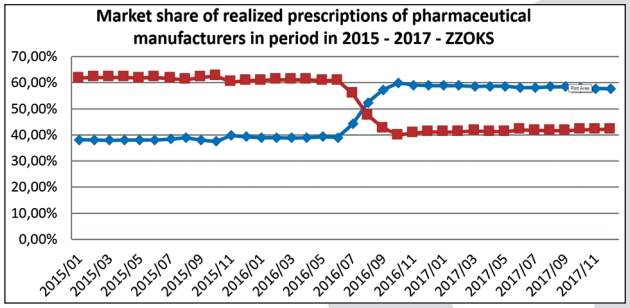
Many pharmaceutical companies have been represented on the essential list of medicines for years, with the prices of medicines being much higher in relation to the environment. The marketing impact of pharmaceutical companies on the presence and share on the essential list has been present for years and the ratios and share of foreign and domestic can be seen in the following graphs 1 and 2.



(blue/ domestic; red/ foreign)

Graph 1. Market share of pharmaceutical manufacturers in the period 2015-2017

The chart shows that the market share of foreign pharmaceutical manufacturers decreases, before the change of the list it ranged between 70% and 80%, and after the change of the list it is in the range between 60% and 70%, while the market share of domestic pharmaceutical manufacturers increases with the change of essential lists from June 2016, from 20% to 30%, to 30% to 40%.



(blue/ domestic; red/ foreign)

Graph 2. Market share of realized prescriptions of pharmaceutical manufacturers in the period 2015-2017

When it comes to the realization of prescriptions of pharmaceutical manufacturers, the situation is different, the realization of prescriptions until June 2016 was 60% of foreign producers and 40% of domestic producers. With the adoption of the new list, there was an inverse ratio of the realization of recipes, where there is a decrease in the realization of foreign recipes from 60% to 40%, and an increase in the realization of recipes from domestic producers from 40% to 60%.

In order to illustrate the effects of the change in market share following the implementation of the new list from June 2016, the following data (chart 3) are presented:

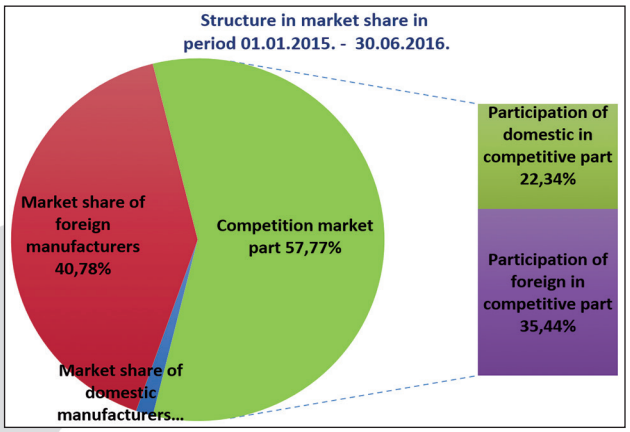


Chart 3. Presentation of the structure of market participation for the period 01.01.2015. – 30.06.2016.

The graph shows the situation before the change of the essential list of medicines and which appears to follow the market share of domestic producers which is only 1.48%, then the market share of the foreign manufacturer's is 40.78%, followed by the participation of domestic and foreign in the competitive part which occupies 57.77% of the market share for the period 01.01. 2015 - 30.06. The chart shows very little participation of domestic producers on the list of only 1.48%, although they also have a share in common competitive part with 22.34%, but this is a small amount that does not exceed the total even 30% of the presence on the essential list of medicines. Foreign producers are represented with 40.78% in the part of the market where they have no rivals, as well as in the competitive part

Table 1. Demonstration of the participation of domestic and foreign producers in the total turnover expressed in BAM in the period 2015-2017

Period	01.01.2015. - 30.06.2016.	01.07.2016. - 31.12.2017.
Total turnover of producers	**94.880.365**	**87.517.296**
Participation of domestic producers	22.587.240	30.264.424
Participation of foreign producers	72.293.125	57.252.872
Part where both domestic and foreign producers have medicaments (competitive parts)	**54.797.431**	**49.603.747**
Participation of domestic in competitive part	21.185.818	28.445.587
Participation of foreign in competitive part	33.611.613	21.158.160
Total part / competitive part	57,77%	56,68%
Part of expenses without presence of domestic producers	1.401.422	1.818.838
Part of expenses without presence of foreign producers	38.681.512	36.094.711

with 35.44%, which totals 76.22%, therefore much more compared to domestic producers.

The following chart presents the situation after the change of the essential list of medicines:

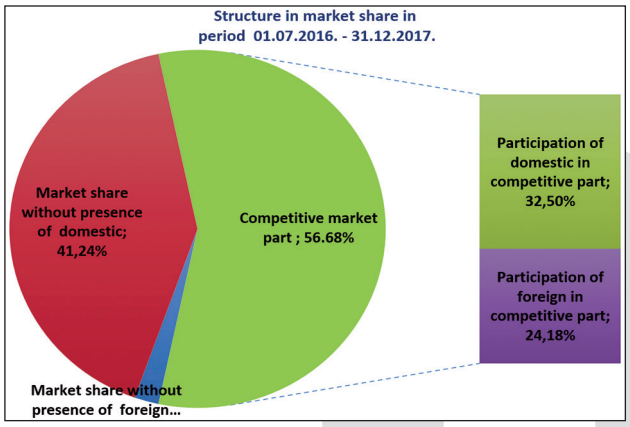


Chart 4. Presentation of the structure of market participation for the period 01.07.2016. – 31.12.2017.

The graph shows that the market share of domestic producers increased from 1.48% to 2.08%. Also in the competitive part increased the share of domestic from 22.34% to 32.50% for the specified periods before and after the change of the essential list. However, despite the preferences of domestic producers on the list, the share of domestic products is not significantly increased because in our domestic assortment we do not have all the medicines represented on the essential list, as well as because we import quite expensive medicines of foreign manufacturers, which must be present on the list because they are considered essential. As for the foreign manufacturers in the competitive part of the chart it is shown that they are represented with 24.18%, and were 35.44% before preferences of domestic producers, so in this part we have decrease of foreign producers by 11.26% for the period. This decline of foreign manufacturers led to an increase of domestic producers by 10.16%.

In order to monitor the tendency of market participation, a presentation of market participation for the period 2011-2017 was presented below.

It is noted that the percentage of foreign producers is twice bigger than the percentage of domestic producers on the list. It shows decrease in the percentage of foreign producers by some 5%, and 5% increase in domestic participation in 2017 in comparison to 2016. If we look at the average value of foreign producer in the past period which is 71.41%, it is significantly higher by 42.82% compared to the domestic average whose average of participation was 28.59%.

When we split the market into individual producers, then we can better spot the differences before and after domestic preferences. Table 3 shows the manufacturers in alphabetical order with their participation. Producers who are represented on the essential list of The Canton of Sarajevo, which did not cross 1% of the market participation are classified as others. For each domestic producer, growth can be seen in 2016 and 2017 compared to 2015 (Bosnalijek, Farmavita, Hemofarm), as can be seen in the table 3.

Concerning the foreign manufacturers, the most changes were happened with Krka, Lek and Plive, whose percentage of participation in market share in 2017 did not exceed even 1%. In this table we also have foreign manufacturers whose share has increased in 2016 and 2017, but this is about putting their new medicines on the list, as well as increased prescription of existing medicines, such as MSD, Novartis Pharma, Novo Nordisc.

Table 4. shows the consumption of medicines from the essential list in the Canton of Sarajevo according to age. The number of insured persons refers to data from the Records of the Institute of Health Insurance that were registered on compulsory health insurance on a day 31st of December of specific year.The table shows that the number of insured people grew year-on-year, with the exception of 2017 when fewer than 2.430 insured people were reported in compairson to 2016.

In the table 5 is shown the consumption of medicines for the period 2011 to 2016 for medicines for essential lists of medicines, ampuleted

Table 2. Presentation of the percentage participation of domestic and foreign producers for the period 2011-2017.

Producers	2011	2012.	2013.	2014.	2015.	2016.	2017.
Domestic	32,63%	29,22%	26,11%	23,77%	24,10%	29,62%	35,61%
Foreign	67,37%	70,78%	73,89%	76,23%	75,90%	70,38%	64,39%

Table 3. Presentation of the precentage participation of pharmaceutical producers for period 2011/2017.

Producers	2011.	2012.	2013.	2014.	2015.	2016.	2017.
Abbott	2,07%	2,08%	2,32%	2,39%	2,37%	2,73%	2,72%
Alkaloid	1,71%	3,18%	3,67%	3,95%	3,93%	2,92%	1,32%
Berlin Chemie	3,38%	3,54%	3,44%	3,38%	3,19%	2,44%	2,64%
Bosnalijek	25,89%	20,94%	16,50%	13,38%	12,91%	14,79%	16,57%
Eli Lilly	5,79%	4,52%	3,79%	3,61%	3,52%	3,74%	4,35%
Farmavita	4,96%	5,59%	6,72%	7,50%	8,56%	11,37%	14,09%
Gsk	5,74%	5,58%	5,57%	5,26%	4,47%	4,07%	4,01%
Hemofarm	1,45%	1,87%	1,98%	1,83%	1,62%	2,05%	2,56%
Krka	8,18%	9,49%	9,48%	6,98%	7,00%	4,98%	0,25%
Lek	2,25%	1,80%	1,95%	2,16%	2,71%	1,77%	0,13%
Msd	3,12%	2,87%	3,18%	5,17%	5,90%	5,77%	6,12%
Nobel	1,15%	1,33%	1,68%	1,87%	1,90%	1,38%	0,35%
Novartis Pharma	1,48%	1,61%	2,44%	3,55%	4,49%	6,58%	7,19%
Novo Nordisk	6,68%	6,48%	7,31%	8,02%	7,63%	7,13%	7,57%
Phizer	0,92%	1,90%	2,41%	1,80%	1,84%	1,67%	1,93%
Pliva	3,62%	3,83%	2,98%	2,91%	2,57%	1,81%	0,54%
Sanofi Aventis	8,55%	8,81%	8,77%	8,46%	7,62%	7,98%	8,46%
Takeda	3,21%	3,63%	3,44%	3,46%	3,22%	2,41%	1,48%
Others	9,85%	10,95%	12,37%	14,32%	14,55%	14,41%	17,72%

Table 4. Consumption of medicines from the essential list in The Canton of Sarajevo for the period 2011-2017.

Year	The financial amount of the essential list of medicine expressed in (KM)	Number of insured persons
2011.	53.025.756	414.566
2012.	57.161.642	421.962
2013.	59.798.476	420.880
2014.	62.320.766	422.235
2015.	66.674.441	427.359
2016.	67.807.174	430.900
2017.	56.995.853	428.470
Altogether	**418.742.934**	

Table 5. Total consumption of medicines expressed in convertible marks and number of insured persons for period 2011 to 2016.

Description	2011	2012	2013	2014	2015	2016
Number of insured persons	414.566	421.962	420.880	422.235	427.359	430.900
The essential list of medical products	53.025.756	57.161.642	59.798.476	62.320.766	66.674.441	67.807.174
Ampulated medicines products	1.748.040	1.844.766	1.919.723	2.182.197	2.335.058	2.718.822
Medicines ouf of list (refund)	205.083	211.480	231.825	154.387	72.147	171.940
Fees	7.789.492	8.412.489	8.540.257	9.041.669	9.588.361	8.889.229
Altogether	**62.768.371**	**67.630.377**	**70.490.281**	**73.699.019**	**78.670.006**	**79.587.166**

medicines products, medicals that were refund because they are not on the essential list, service charges for prescriebed medical products on issued prescriptions (here are also included the costs of paying on-call for public pharamacies "Public Institution Apoteke Sarajevo" because only those on call are in The Canton of Sarajevo), as well as the number of insured persons for specific period.

Of the total consumption of drugs, the largest share of cost belongs to medicines from the essen-

tial list of drugs. Since the consumption of medicines increased from 62 million BAM to 79 million BAM for the period, consumption was analyzed per year. The largest share of cost of medicines for 2011 was with medicines on the essential list of prescription drugs, which in the structure of the total cost of medicines account for 84.5%. The cost of ampulated drugs used in health institutions in accordance with the List of ampulated drugs amounted to 1,748,040 BAM and in the total cost of medicines participated in 2.8%. In 2011, the fee for contract pharmacies for issued medicines was 7,789,492KM and total drug costs had a share of 12.4%. The fee for contract pharmacies is set in the amount of 1,90 BAM per prescription. For ampuleted medicines was calculated a margin of 6% on the fixed price of medicine. Total costs for medicines in 2011 were 62,768,371 BAM to 414,566 insured persons.

The total costs of medicines in 2012 were 67,630,377 BAM (to 421,962 insured persons), and are 8% higher than the previous year. The table shows that the highest share of cost for medicines belongs to the essential list of medicines, which is 57,161,642 BAM, which is a percentage of 84.5%. The cost of ampulated medicines was 1,844,766 BAM, which is a percentage of 2.7% of the total cost of medicines, and otherwise these drugs are used in health facilities according to the List of Medicines. Then, the table is followed by the amount of 8.412.489 BAM which refers to the prescription fee to refund the pharmacy for issued prescriptions in the amount of 1,90BAM per prescription and fees for on call pharmacies of public institutions is in the amount of 6%. This cost is in an estimated amount of 12.5% of the total cost. Medicines approved upon request amount to only 0.3% in total cost amount, i.e. 211,480KM.

The total costs of medicines for 2013 amounted to 70,490,281 BAM (to 420,880 insured persons), which is 7,490,281 KM more than the planned amount, as a result of excessive prescribing medicines. The planned funds for the medicines amounted to 63,000,000 BAM, a much higher cost than it was planned. A new list of medicines was revised and adopted, but which began in the last quarter of 2013, so it could not even provide some significant results of rationalization. The largest share of medicines costs are medicines from the essential list of medicines in the amount of 59,798,476 BAM (value with VAT free of charge for issuance), which in the structure of the total costs of medicines make up 84.8%. The costs of ampulated medicines used in health institutions in accordance with the List of Ampulated Drugs were realized in the amount of 1,919,723 BAM and in the total cost of medicines participated with 2.7%. The fee for contract pharmacies for issued medicines in 2013 was 8,540,257 BAM and in the total cost of medicines has a share of 12.1%. Medicinal products which are not included in the List of Medicinal Products approved by the Medicines Commission amounted to 231,825 BAM, which is percentage of 0.3%.

In 2014, expenses for medicines were 73,699,019 BAM (to 422,235 insured persons), which is 4.5% higher than the previous year. The highest proportion is taken by medicines from the essential list of medicines, which account for 62,320,766 BAM. The costs of ampulated medicines amounted to 2,182,197 BAM, costs of refunded medicines in the amount of 154,387 BAM. The fee to contract pharmacies for this year was 9,041,669 BAM.

The cost of medicines in the total amount for 2015 amounts to 78,670,006 BAM (to 427,359 for insured persons), which is 7% higher than the previous year. The table shows that the highest cost was for the issued medicines from the essential list and amounted to 66,674,441 BAM, then the cost for the fees for the issued prescription drugs was 9,558,362 BAM, the cost of ampuleted was 2,335,058 BAM, and the refunded medicines approved by the Commission amounted to 72,147 BAM. The table also sees an increase in all costs for medicines compared to 2014, in addition to refunded medicines. Compared to 2014, costs for medicines in 2015 increased by 4,970,988 BAM.

Total drug costs for 2016 were 79,587,166 BAM (on 430,990 for insured persons), which is 1% less than the planned funds for 2016.

The table showed the consumption of medicines from the essential list totalling 67,807,174 BAM, followed by the consumption of ampulated drugs in the amount of 2,718,822 BAM which increased if it is compared to the previous year, refunds of medicines in the course of 2016 amounted to 171,940 BAM. The fee of prescriptions for presribed medicines was lower in 2016 if we compared to 2015 by 699,132 BAM, as it was reduced from 1.90 BAM to 1.65 BAM in 2016.

To help identify increased drug consumption, the following graphic representation is presented:

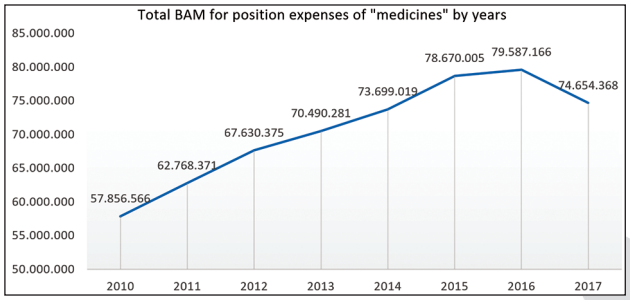


Chart 5. Overview of drug consumption for the period 2011-2017

The chart shows increased drug consumption from 2010 to 2015, and in 2016 it is noticable an upward trajectory of costs, ranged from 57,856,566 BAM in 2010 to 79,587,166 BAM in 2016. For the period of 6 years, consumption increased by 21,730,600 BAM. In 2017, the results of decrease in drug consumption were visible to 74,654,368 BAM or by 4,932,798 BAM if was compared to 2016.

Financial overview of total expenditures of medicines in budget

As it had been mentioned, total spending on medicines in the budget of the Institute of Health Insurance of The Canton of Sarajevo ranged from 19.7% in 2011 to 23.8% in 2016 and up to 21.6% in 2017.

In table 6 are shown the total costs of medicines as well as their expenditures in the budget for the specified period of time.

The table shows that costs for medicines increased from year to year, i.e. from 62,768,371 BAM in 2011, and in 2016 they were 79,587,166 BAM. Due to this constant trend of rising costs for medicines, appropriate measures had to be taken to stop this trend of rising drug costs. In 2016, upward trend of drug costs was stopped with appropriate measures through an integral informational system. In 2017, there was a marked decline in drug consumption, as well as a decrease in drug expenses. The table can also show that the overall movement of expenditure for this period was recorded in the increase of drug expenditure by 4.1% for the same period, and in 2017 there was a decline in drug expenditure, down by 2.2% compared to 2016. The table also shows the total amount of budget of the Institute of Health Insurance of the Canton of Sarajevo.

Discussion

Pharmaceutical companies have struggled with marketing models to take as much of the essential list as possible in the Canton of Sarajevo, since the Federal List was with generic names, and then the list at the canton level is formed with protected names.

In addition to the conditions that manufacturers must have in order to be on the list in the first place, the influence of the promotion by the manufacturer is also significant. It was often known to happen in the past period, that one manufacturer lowered the price much more than it should, only to be present on the list, and then on the basis of this, was formed drug price for this generic, so the other manufacturers had to lower prices, which led to a significant decrease in prices in the last period, resulting in savings in the budget.

By June 2016, the share of pharmaceutical manufacturers was in favour of foreign producer whose representation on the list was between 70% and 80%. With the adoption of a new list and preferences of domestic contractors, this ratio changes, and the share from 20% to some 40%, and the producer's share is also reduced to 60%. However, this ratio can no longer be changed as the most medicines that are more expensive and more innovative do not have production in our country and but must be imported, such as in e.g. insulin.

Table 6. Presentation of total consumption of medicines and their expenditures in the total budget of the Institute of Health Insurance of The Canton of Sarajevo

Description	2011.	2012.	2013.	2014.	2015.	2016.	2017.
Total medicines cost	62.768.371	67.630.377	70.490.281	73.699.019	78.670.006	79.587.166	74.654.368
Participation in total expenditure (%)	19,7	20,0	21,43	22,16	23,7	23,8	21,6
Budget amount (BAM)	316.206.860	330.979.233	320.256.227	356.967.329	341.655.755	350.121.250	368.995.444

An evident increase in consumption for medicines from 53,025,756 BAM in 2011 to BAM 53,025,756 in 2013. 66,674,441 BAM in 2015 and this growth trend continued in the first half of 2016, which is why measures were taken to rationalise drug consumption, and the correcting of the essential list, the introduction of restrictions, as well as "e Direction". Due to all of this trend of growth in drug consumption stopped in 2016, but the results were only felt in the last quarter of 2016, as many three-monthly therapies were prescribed in the third quarter of 2016. In 2017, the results of the list revision and the introduction of restrictions and guidelines are significant, as can be seen from the reduced consumption of essential list medicines in 2017, in which consumption decreased by 5,770,147 BAM or by 9.2% in comparison to 2016.

In October 2015, the Government of The Canton of Sarajevo adopted a new Decision on positive, hospital and master list of medicines of the Sarajevo Canton. The new list in comparison to the previous list (which was adopted at the end of September 2013 with amendments from December 2013) differs in its content of A and B list medicines primarily in the part of List B where a significant number of drugs that were not an integral part of the Federal list were taken off the list. At the same time, a number of drugs, which have been placed on federal lists A and B, have now been placed on the Sarajevo Canton lists. A small number of B-list drugs have changed the share recognized by Institute.

All revisions of the Federal list seem to be on the same principle, which is to reduce the prices of individual drugs from the list, but at the same time design and set new drugs.

Potential savings from reducing the prices of existing listed medicines are offset (or even exceeded) by generating the cost of new medicines. It is particularly interesting and symptomatic that in most cases it is not drugs that treat some diseases for which there were no drugs on the Federal list before, but are newer (but also drastically) more expensive drugs that treat the same diseases for which there were previously drugs on the list. This is particularly striking in the field of oral antidiabetics, where every time the Federal list is revised, 2-3 new generics are added, the price of which is drastically higher than the previous ones.

Conclusion

The drug market is highly regulated, because health has the status of the public good. The drug market does not operate with the usual laws of supply and demand and do not depend on market prices. Demand for medicines is affected by demographic changes in population structure, chronic diseases, introduction of new innovative drugs, the supply of drugs is carried out according to the laws of regulation of the drug market.

Medicaid spending in the Health Insurance Institute's budget increased year-on-year and reached 23.8% in 2106. For this reason, key measures of rationalization, recording of consumption and control of drug consumption through the integral information system "ezOblak ZZOKS" ("eGuidelines" and "VDT") have been taken, enabling the patient to be monitored through the system.

In 2017, drug expenditure was reduced with measures taken and amounts 21,6%.

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The relationship between Post Tetanic Count and Train of Four responses at the terminal stage of the neuromuscular block caused by Rocuronium in patients administered infraclavicular block with the help of ultrasonography after general anesthesia

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Abstract

Neuromuscular blockers are commonly used in anesthesia practices. The purpose of this study is to research the relationship between PTC and Train of Four (TOF) response at the recovery stage of rocuronium- and infraclavicular-block-based motor, neuromuscular blockage in patients for whom infraclavicular block has been done for the purpose of general anesthesia and analgesia.

Study was conducted over 60 patients taken in for orthopedic arm and forearm surgery.

Our study found a close relationship between PTC and T1 time in accordance with previous observations made with other non-depolarized neuromuscular blocking medications.

Key words: Neuromuscular blockers, Post Tetanic Count, Infraclavicular block, Train of Four, Rocuronium

Introduction and Purpose

Neuromuscular blockers (NMB) are commonly used in anesthesia practices. Simple methods are desired to monitor its effects. Therefore, anesthetics traditionally assess the degree of neuromuscular block only compared to the clinical benchmark. Instead, Post Tetanic Count (PTC) is an established method to stage the compilation during intense neuromuscular block. (1) It has been proven that neuromuscular junction (NMJ) monitors are beneficial auxiliaries in the practice of clinical anesthesiology. The recommendation for the administration of neuromuscular monitoring for patients receiving NMB is based on two important topics: First is because of the variable individual response given to muscle relaxers, and second is because of the narrow therapeutic window. (2) Single spasm, tetanic, or train of four (TOF) can be used when no response is received for stimulation to assess the intensity of the neuromuscular blockage and can be used to estimate the time in which the first spasm in TOF (T1) is expected to emerge again. Following the implementation of neuromuscular block agents, there was no perceivable block up to 75-85% of the receptors, and paralysis was completed at 90-95% receptor fullness. (3) For this reason, adequate muscle relaxation corresponds to a receptor fullness rate of 85 to 90%. A close correlation was found between PTC and TOF compilation in the neuromuscular blocks provided by pancuronium (4), vecuronium (5), atracurium (6), and rocuronium (7). Sugammadex is a prime antagonist of aminosteroidal neuromuscular blocking agents (NMBAs), especially rocuronium; Before the introduction of sugammadex, however, the indirect mechanism of antagonism of the rocuronium-induced neuromuscular block has a ceiling effect, and is limited by the depth of the neuromuscular block at the time of reversal. (8)

Recovery of neuromuscular blockade is monitored through responses of the innervated muscle under indirect neuronal stimulation particularly that of the ulnar nerve at the wrist level and the adductor pollicis muscle. (9) Patients with partial neuromuscular block usually show TOF and the TOF ratio of < 0.7. TOF ratio of >0.9 by mechanomyography or electromyography-type monitor and that of > 1.0 by acceleromyography-type monitor are considered as complete recovery. (9)

Infraclavicular block can be used for post-operative anesthesia in patients.(10) More than 40%

of patients subjected to orthopedic procedures on foot experience moderate to severe postoperative pain. (11) Single-injection brachial plexus neural blockage, like infraclavicular block, provides analgesia for an average of 12-14 hours after the upper-extremity procedure. both lateral and medial Infraclavicular blocks with multiple injections can provide excellent surgical conditions, it was shown in clinical studies that lateral Infraclavicular blocks with triple-injections of local anesthetic around the axillary artery was not superior to a single-injection technique. (12, 13)

After analyzing the block, most patients need narcotics for pain control. But the tolerance of narcotics can have some powerful side effects like sedation, itchiness, nausea, and vomiting. Knowing the PTC/T1 Specific relationship during the removal of the block can allow for more sensitive neuromuscular monitoring during the recovery from the block in patients for whom rocuronium and infraclavicular block was administered.

The purpose of this study is to research the relationship between PTC and TOF at the recovery stage of rocuronium- and infraclavicular-block-based motor and neuromuscular blockage in patients for whom infraclavicular block has been done for the purpose of general anesthesia and analgesia.

Materials and Methods

Of the 60 ASA I and II adult patients, orthopedic patients for whom endotracheal intubation and muscle relaxation were requested under general anesthesia and whose arms and forearms requiring analgesia were to be worked with during and after surgery were included in the study after obtaining ethics board and patient approvals. Those with neuromuscular disorders and those who use medications that inhibit neuromuscular block were excluded from the study.

TOF monitorization began by performing induction for the patients with an initial 2 mg/kg Propofol and 1.5 µg/kg fentanyl. The stimulated response data were constantly displayed and were also recorded onto a disc for later analysis. The supramaximal stimulation and response stabilization after the five-second 50 Hz tetanic stimulation were observed. 0.5 mg/kg rocuronium was administered intravenously after calibration over 5-10 seconds. The responses to TOF stimulation were recorded once every 15 seconds, measured from the alignment of the ulnar nerve in the wrist. When it was seen that the response disappeared entirely, endotracheal intubation was performed.

While the patient was in a supine position after endotracheal intubation, their head was turned to the other side for the region to be administered with the block. The arm to which the block was to be administered was brought to adduction and the block was placed on the chest of the patient in a state of flexion. Following the disinfection of the region with polyvinylpyrrolidone iodine, the Ultrasonography (US) probe (Esaote LA435 linear probe, 10-18 MHz, Florence, Italy) is placed longitudinally on the recommended region to implement lateral sagittal infraclavicular block (LSIB) in a sterile manner. (14) The G-nerve stimulation needle (Pajunk, Geisingen, Germany) at a length of 80 mm was directed toward a 7 o'clock alignment compared to the artery at the same plane as the US probe when the axillary arterial veins and brachial plexus cords were displayed. When it was observed that dissemination was suitable by providing first 2 ml local anesthetic, the remaining local anesthetic was given in the form of doses for fractions by performing negative aspiration in intervals. The trio injection method was administered, being viewed with the ultrasonography over which local anesthesia was properly spread around each cord (lateral, posterior, medial). (14) For a single extremity, 10 ml 2% lidocaine (to include 5 µg. ml-1 adrenaline) + 10 cc 7.5% levobupivacaine were given. The post-tetanic stimulation was administered based on the previously programmed series.

A 3-second pause was done after the 50-Hz tetanic stimulation for 5 seconds after the 15 pretetanic 1-Hz single spasm during the TOF stimulation, and 15 post-tetanic 1-Hz stimulations were administered. This cycle was repeated with the TOF stimulation restarted once every six minutes 15 seconds after the last post-tetanic stimulation. The patients were separated into two random groups based on technique used for the anesthesia maintenance. A propofol infusion from 100-200 Mg/kg-1 and a mixture of 50% N20 and O2 were used for the maintenance of anesthesia in Group 1 (n=30 patients), while desflurane and a mixture of 50% N2O and O2 were used in Group 2 (n=30 patients).

The time that passed from the administering of the rocuronium to the emergence of the post-tetanic responses and the time of the reemergence of the first spasm in TOF were recorded.

The correlation between post-tetanic response count and time interval that passed until TM1 was evaluated. All the statistical analyses were performed in the SPSS 22.0 program. $p<0.05$ was accepted as statistically significant.

The Student t-test and Mann-Whitney U test were used to determine the significant differences in the demographic characteristics between the two groups.

Results

There was no significant difference between the two groups in terms of age, gender distribution, height, weight, or ASA physical condition. (Table 1)

Table 1. Demographic Data

	Group 1 n=30	Group 2 n=30	P Value
Age (yr)	44.8±11.4	43.6±9.4	0.641
Males	18	12	
Females	12	18	0.12
Height (cm)	167.8±12.2	167.4±9.6	0.882
Weight (kg)	75.7±9.6	78.1±12.3	0.412
ASA I	13	14	
ASA II	17	16	0.795

Time for a single response to the post-tetanic stimulation (PTC1) was calculated from the administering of the rocuronium in the patients for whom only a single response was recorded because post-tetanic stimulation is administered in six-minute intervals.

Table 2. Comparison of neuromusculer effects of rocuronium

Time of appearance (min)	Group 1	Group 2	P value
PTC1	35.6±7.8	39.5±6.8	0.068
T1	46.9±6.5	56.7±5.4	<0.0001
PTC at T1	8.3±0.5	9.3±1.7	<0.025

These data were obtained in 21 patients in Group 1 and 24 patients in Group 2. The length of time that passed from the rocuronium injection to a single response in Group 1 was 35.6 ± 7.8 minutes while it was considered to have occurred during the post-tetanic stimulation (Table 2).

The length of time that passed from the rocuronium injection to the first identification of T1 was 46.9 ± 6.5 minutes. The average duration between the reemergence of the first spasm in PTC1 and TOF (T1) was 11.3 ± 1.9 and within 10-18 minutes, and had a median value of 10 minutes. When T1 emerged again, between eight and nine responses could emerge against the post-tetanic stimulation. T1 was not observed in any patient in the 10-minute PTC1 section. The average length of time for PTC1 was 39.5 ± 6.8 minutes in Group 2.

This length of time was not significantly different than what was observed in the patients treated with propofol (Group 1). The reemergence time for T1 in Group 2 (56.7 ± 5.4 minutes) was significantly longer than what was observed in Group 1 ($p<0.0001$). The average length of time that lasted from PTC1 to the reemergence of T1 was 16.5 ± 4 minutes (median 16 minutes), and distribution was 12-30 minutes. When T1 emerged again, between eight and 14 post-tetanic stimulation responses could emerge. Table 2 shows the various different lengths of time (SD±) compared to T1 and PTC1.

There was a good correlation between PTC and T1 return in both groups. The relationship with PTC after 0.15 mg/kg rocuronium was given and time for T1 improvement occurred at r±0.92 for group 1 and r±0.78 for group 2. (Figure 1)

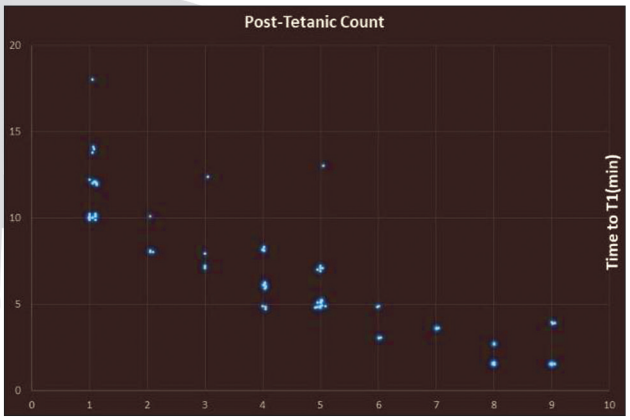

Figure 1. PTC and Time to T1 (min)

Discussion

The results of this study reveal the relationship between number of responses and time interval given for post-tetanic stimulation until the initial response is received for TOF stimulation during recovery from neuromuscular and infraclavicular block induced with rocuronium. The PTC / T1 time relationship was demonstrated with other nondepolarizing neuromuscular blocking medications and is special for each medication. (4-6) The period acquired from administering rocuronium up to PTC1 was not affected by the technique used. Similar findings were reported with other neuromuscular blocking medications. (15) A potential explanation for this finding is that the process of post-tetanic facilitation is a presynaptic phenomenon that occurs in the motor nerve endings that are not inhibited with inhaled anesthetics. (16) However, the time interval from the application of the rocuronium up to T1 extended with the use of desflurane and infraclavicular in terms of propofol that prolongs the time interval between PTC1 and T1 in these patients. (Group 2) Inhaled anesthetics fundamentally strengthen the neuromuscular blockage through a postsynaptic effect, and this in turn affects the improvement of the spasm after TOF stimulation. (17) The prolongation of the PTC1 / T1 interval with an inhaled anesthetic has previously been described. (18)

In our study, we conducted neuromuscular monitoring using acceleromyography. The comparisons between the results of past studies with the present findings should define the potential differences that could be attributed to the selection of monitoring techniques. However, studies have shown that there is a good relationship between the measurements and acceleromyography and electromyography. (19, 20) The tetanic stimulation must not be implemented more frequently than six minutes. Otherwise, local physiological changes in the neuromuscular synapse can reflect incorrect information about the status of the neuromuscular transfer. (4) Because there is no constant PTC monitoring and because a series of stimuli need to be used before the count, the response might have occurred simultaneously during the stimulus or one minute before, and the real value was therefore ignored. These limitations might have affected the precision of our results by up to +/- 60 seconds.

The PTC method is a method of single-nerve stimulation that helps the clinician quantitatively assess intense neuromuscular blockage. The advantage of this monitoring technique is clear when it is important to avoid the spontaneous movements of the respiratory muscles. PTC monitoring allows for the early estimation of when the response to TOF stimulation will emerge after tracheal intubation, which is facilitated by rocuronium. The absence of a response to Post-tetanic stimulation (PTC0) shows that the neuromuscular blockage is still intense and that it will take at least 10 minutes to observe a response to TOF stimulation. To the contrary, a PTC with a value of 8 shows that the response to be given to TOF is close. Hiccups, tickles, and coughs may occur during the surgical procedure even though the TOF responses are removed in the wrist. (21) When these types of motions must be avoided during anesthesia, PTC can be used to measure the more intense, necessary blockage to provide for diaphragm paralysis. The initiation of neuromuscular recovery is prevented by administering only a maintenance dose thanks to the measurement, and the opportunity is presented to maintain adequate muscle relaxation. In another clinical application, the PTC / T1 relationship can be used toward the end of the surgery if there is no response to the TOF stimulation. During nondepolarizing neuromuscular blocking agent (like Rocuronium)-induced neuromuscular blockade, TOF fade and TOF ratio are considered as phenomena related to the presynaptic neuronal nicotinic acetylcholine receptors (nAChRs). (22, 23) A recent study reported that these phenomena are related to the postsynaptic receptor type. (23) PTC shows how long the initiation of the reversal in the neuromuscular junction will last (at least in the form of one or two responses to the TOF stimulation). Meanwhile, the anesthesiologist guided by the post-tetanic response can make a conscious decision about whether to administer a maintenance dose of the neuromuscular blocking medication based on the expected end of the surgery.

Conclusion

We researched the relationship between the reemergence of PTC and T1 during recovery from neuromuscular blockage originating from intense rocuronium in 60 patients who received both propo-

fol and desflurane anesthesia and were administered infraclavicular block. Our study found a close relationship between PTC and T1 time in accordance with previous observations made with other non-depolarized neuromuscular blocking medications.

PTC monitoring in the administering of infraclavicular blockage in addition to neuromuscular blockage caused by intense rocuronium helps the clinician assess the intensity of the blockage in the correct manner and estimate the period of improvement up to T1. Nevertheless, more studies are needed to establish the best target of the TOF count to provide necessary and sufficient muscle relaxation during recovery from neuromuscular blockage originating from intense Rocuronium and administered infraclavicular block.

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Skin changes and metabolic control parameters in patients with diabetes melitus type II

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Abstract

Introduction: to determine the correlation of metabolic control parameters with the appearance of skin changes in patients with type II diabetes mellitus.

Respondents and methodology: a cross-sectional study in 200 subjects, aged 20-60 years, both sexes, suffering from type II diabetes mellitus, analysed the association of metabolic control parameters with skin changes associated with diabetes. Respondents were divided into four groups. Group 1 patients with skin changes with a greater or lesser connection with diabetes mellitus, group 2 patients with infections, group 3 patients with skin manifestations of diabetic complications and group 4 patients with allergic reactions to antidiabetic therapy. The level of metabolic control was assessed based on the values of glycemia, HbA1C, cholesterol, triglycerides, HDL and LDL.

Results: Skin conditions from group 3 had a significant but poorly expressed correlation with HbA1c values (positive correlation) and with HDL values (negative correlation). Skin conditions from group 2 had a significant, positive and poorly expressed correlation with HDL values. The frequency of skin changes between subjects categorized according to metabolic control parameters was compared. In these analyses, a statistically significant difference was found in the frequency of skin changes by groups for triglyceride values. (p=0,0028). Though skin changes were more present in patients with pathological values of metabolic control parameters, no statistically significant difference was found by groups. (p>0,05).

Conclusion: unregulated values of metabolic control parameters have a significant role in the development of skin changes in patients with type II diabetes mellitus.

Key words: diabetes mellitus type II, metabolic control parameters, skin changes.

Introduction

Type II diabetes mellitus is a chronic metabolic disease caused by multiple causes, and is characterized by constantly increased blood sugar values and disorders in the metabolism of carbohydrates, fats and proteins due to absolute or relative lack of insulin activity - resistance or a combination of both mechanisms.

Skin changes in patients with type II diabetes mellitus can occur as part of diabetic and metabolic disorders or diabetic complications (microangiopathy, macroangiopathy, polyneuropathy). The incidence of skin changes in diabetes mellitus ranges from 30% to as high as 100% depending on the duration of the disease (1).

Diabetes-related skin changes can be divided into four main groups:

1) changes with a greater or lesser association with diabetes;
2) skin infections;
3) cutaneous manifestations of diabetic complications;
4) allergic reactions to antidiabetics (2).

Some authors add a fifth group, endocrine syndromes with skin changes and diabetes, which include migrating necrotic erythema in glucagonoma, skin atrophy, stretch marks and hirsutism in Cushing's syndrome, thickened skin and increased sweating in acromegaly, ataxia telangiectasia, symptomatic prurigo in endocrine diseases, lipodystrophy in rare endocrine syndromes, and diabetes (3). The first group, where there are changes with a greater or lesser connection with diabetes, includes: diabetic dermopathy, prurigo, granuloma annulare, lichen ruber planus, dermatitis bullosa diabeticorum, scleredema adultorum, perforative dermatoses. The second group includes infections with bacteria, fungi, viruses and infestations such as scabies. The third group includes diabetic com-

plications with ulcerations, onychodystrophy, alopecia, effluvium, and xerosis of the skin. Allergic and non-allergic skin changes in diabetics caused by drug therapy belong to the fourth group.

The goal of diabetes treatment is to achieve not only targeted glycaemic but also metabolic control. With the achievement of the target metabolic control, the beginning of chronic complications of diabetes is delayed. Target metabolic control includes: Blood Glucose on an empty stomach: 4-6 mmol/l, ppGUK : 4-8 mmol/L, Blood Glucose at bedtime 5-7 mmol/l, HbA1C less than 6.5%, ideal body weight BMI 19-25 kg/m^2, lipid status: triglycerides <1.7 mmol/l, LDL cholesterol <3 mmol/l, if CHD <2.5 mmol/l, HDL> 1, total cholesterol <4 mmol/l, optimal blood pressure (less than 125/85 mmHg) , smoking cessation (4).

The aim of the study was to determine the association between metabolic control parameters and the occurrence of skin changes in patients with type II diabetes mellitus.

Respondents and methods

The research was conducted at the Department of Skin and Venereal Diseases of the Cantonal Hospital "Dr. Irfan Ljubijankić" in Bihać. The cross-sectional study analysed the association of metabolic control parameters with skin changes associated with diabetes in patients with type II diabetes mellitus, aged 20-60 years, both sexes. The study included 200 subjects who were divided into four groups according to the type of skin changes associated with diabetes. The first group consisted of patients with skin changes with a greater or lesser connection with diabetes mellitus, the second group of patients with infections, the third group consisted of patients with cutaneous manifestations of diabetic complications and the fourth group of patients with allergic reactions to antidiabetic therapy. The purpose of the research was explained to all respondents, written consent was obtained for participation in the research, anamnesis was taken, dermatological examination of the skin and visible mucous membranes was performed. Laboratory tests were performed to determine the degree of metabolic control: glycaemic value, HbA1C, cholesterol, HDL, LDL and triglycerides. The method of spectrophotometry was used for the determination of cholesterol, triglycerides and Blood Glucose, HbA1C- inhibition of latex agglutination, and for HDL and LDL enzyme test on the Beckman AU 480 chemistry analyzer.

Measurements taken for unregulated values of metabolic control parameters were: glycaemic value on an empty stomach > 6mmol/l, HbA1C> 6.5%, total cholesterol> or = 4mmol/l, LDL cholesterol> or = 3 mmol/l, HDL cholesterol <or = 1mmol/l, triglycerides> or = 1.7 mmol/l (4).

Statistical analysis

Statistical analysis was performed in the software package SPSS 22.0 (Armonk, NY: IBM Corp). Descriptive statistics parameters were used to display the basic characteristics of the sample. The chi-square or Fisher test was used to compare categorical variables. The association of skin changes with metabolic control parameters was tested using Sperman's correlation coefficient. The level of statistical significance of 95% ($p < 0.05$) was considered as the limit of significance for all statistical tests.

Results

In the entire sample, a prospective study examined 200 subjects, 122 (61%) female and 78 (39%) male, mean age (± SD) 64 (9) with type 2 diabetes mellitus with skin changes associated with diabetes, in which a total of 333 different skin conditions have been reported. The mean duration of diabetes (± SD) was 123 (80) months and ranged from 3 to 360 months.

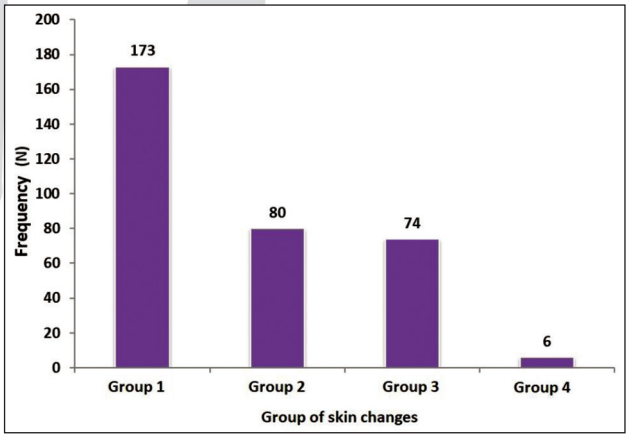

Photo 1. The frequency of skin changes depending on which of the 4 classification groups they belong to

The frequency of skin changes, taking into account which of the 4 classification groups they belong to, is shown in Photo 1. Skin changes from group 1 were the most frequent, in 173 (51.95%) subjects, while the lowest frequency were skin changes from group 4 in 6 (2.88%) subjects, the difference was statistically significant for (p <0, 05).

Metabolic control parameters were correlated with the appearance of skin changes in patients with type II diabetes mellitus. Skin conditions from group 3 had a significant but poorly expressed correlation with HbA1c values (positive correlation) and with HDL values (negative correlation). Skin conditions from group 2 had a significant, positive and poorly expressed correlation with HDL values (Table 1). The frequency of skin changes between subjects categorized according to metabolic control parameters was compared. In these analyses, a statistically significant difference was found in the frequency of skin changes by groups for triglyceride values (p=0,0028). Although skin changes were more present in patients with pathological values of metabolic control parameters, no statistically significant difference was found by groups. (p>0,05) (Tables 2-7).

Table 1. Correlation of metabolic control parameters and skin changes in patients with type II diabetes mellitus

		GUK	HbA1c	triglyceride	cholesterol	HDL
Number of different skin conditions associated with DM	Correlation coefficient	.060	.051	.077	.038	-.021
	p-value	.402	.474	.276	.595	.767
Group 1	Correlation coefficient	-.060	-.021	.076	.052	-.099
	p-value	.400	.772	.286	.467	.161
Group 2	Correlation coefficient	.038	-.036	.002	-.019	**.215**
	p-value	.590	.612	.973	.785	**.002**
Group 3	Correlation coefficient	.103	**.151**	.040	.003	**-.165**
	p-value	.148	**.033**	.575	.972	**.019**
Group 4	Correlation coefficient	.081	-.051	-.072	-.001	.100
	p-value	.255	.473	.310	.986	.159

Table 2. Blood Glucose values within the examined groups

Blood Glucose	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
<6	5 (3,9%)	2 (2,7%)	4 (6,0%)	0,0681
>6	125 (96,1)	73 (97,3%)	63 (94,0%)	
Total (N)	130 (100%)	75 (100%)	67 (100%)	

Table 3. LDL values within the examined groups

LDL	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
<3	43 (33,1%)	27 (36,0%)	21 (31,3%)	0,0631
>3	87 (66,9%)	48 (64,0%)	46 (68,7%)	
Total (N)	130 (100%)	75 (100%)	67 (100%)	

Table 4. HDL values within the examined groups

HDL	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
>1	83 (63,8%)	54 (72,0%)	33 (49,3%)	0,178
<1	47 (36,2%)	21 (28,0%)	34 (50,7%)	
Total (N)	130 (100%)	75 (100%)	67 (100%)	

Table 5. Triglyceride values within the examined groups

Triglyceride	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
<1,7	39 (35%)	21 (35,0%)	21 (35%)	0,0288
>1,7	91 (65%)	54 (38,6%)	46 (39,9%)	
Total (N)	130 (65%)	75 (37,5%)	67 (33,5%)	

Table 6. Cholesterol values within the examined groups

Cholesterol	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
<4	32 (69,6%)	20 (43,5%)	15 (32,6%)	0,0966
>4	98 (63,6%)	55 (35,7%)	52 (33,8%)	
Total (N)	130 (65%)	75 (37,5%)	67 (33,5%)	

Table 7. HbA1C values within the examined groups

HbA1C	Number of respondents (N and %)			P value
	Group 1	Group 2	Group 3	
<6,5	24 (18,5%)	16 (21,3%)	7 (10,4%)	0,122
>6,5	106 (81,5%)	59 (78,7%)	60 (89,6%)	
Total (N)	130 (100%)	75 (100%)	67 (100%)	

Discussion

The frequency of skin changes in people with diabetes mellitus according to most studies ranges from 30% to 71%, and according to some over 90%. They most often appear after the primary disease has developed, but they can also appear as the first sign of the beginning of the disease or as a precursor of diabetes (5). In addition, skin changes can present early signs of complications or poor metabolic control of diabetes and cause a reduction in quality of life. Poor glycaemic control as a risk factor for skin changes in type II diabetes mellitus was confirmed in our study in 96.1% of subjects in group 1, 97.3% in group 2, 94% in group 3 and in 100% of subjects in group 4. There was no statistically significant difference in individual groups. According to a study by Nima M. et al. (2013) in a study involving 873 subjects with changes at their feet, most subjects 85.6% had poor glycaemic control and only 14.4% had good glycaemic control. According to Al-Maskari et El-Sading (2007) in a study on the prevalence of risk factors for the development of diabetic complications, only 38% of patients had good glycaemic control, analysing the regulation of glycemia with HbA1C. In our study, HbA1C as a metabolic control parameter was elevated in 81.5% of subjects in group 1, 78.7% in group 2, 89.6% of subjects in group 3 and in 66.7% of subjects in group 4. This difference was statistically significant in the respondents from group 3. Also, in the study of Al-Maskari et El-sading (2007), cholesterol was elevated in 34.4%, triglycerides in 25.2%, LDL in 53.4%, and HDL decreased in 25.7% of subjects. Hyperlipoproteinemia was present in our subjects. We had elevated cholesterol values in 63.6% of subjects in group 1, 35.7% in group 2, in group 3 in 33.8%, and 3.9% of subjects in group 4. Triglycerides were elevated in group 1 in 65%, 38.6% of subjects in group 2, 39.9% in group 3, and 2.9% of subjects in group 4. HDL was reduced in group 1 in 36.2% of subjects, in group 2 in 28%, in group 3 in 50.7%, and in group 4 in 2.9% of subjects. This difference was statistically significant in group 1 and group 3. LDL was elevated in 66.9% of subjects in group 1, 64.0% in group 2, in 68.9% in group 3 and 83.3%) of subjects in group 4. A statistically significant difference was found in the frequency of skin changes by groups for triglyceride values ($p = 0.0028$), while for other values of metabolic control parameters the difference was not significant ($p > 0.05$).

The main goals of diabetes mellitus treatment are to achieve not only targeted glycaemic but also metabolic control, and prevent the development of

late complications by establishing a proper metabolic balance in the body, and achieving conditional health by establishing work ability and inclusion in social life. Diabetes mellitus is treated for life, and therefore the seriousness, commitment and education of patients, as well as active participation in the treatment of the disease are important. Diabetics must be aware of their disease, its possible complications and how to prevent them, and if there are or occur complications, the possibility of their timely treatment. Treatment of diabetes mellitus is an integral part of everyday life and a person with this disease needs the help of a medical team (doctor, nurse, dietitian). Therapy is a complex, dynamic process and involves the education of diabetics, a rational diet, physical activity and medical treatment (8).

Conclusion

Unregulated values of metabolic control parameters have a significant role in the development of skin changes in patients with type II diabetes mellitus.

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Antimicrobial resistance of *Pseudomonas* genus isolates in outpatient infections

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Abstract

Introduction: The *Pseudomonas* genus is one of the most complex bacterial genera and it also belongs to Gram-negative bacteria with the largest number of different species, which keeps growing year after year. There are currently 144 recognized species of the *Pseudomonas* genus, the most important representative of which belongs to the fluorescent group - *Pseudomonas aeruginosa*. Compared to enterobacteria, *P. aeruginosa* is a bacterium that is resistant to antimicrobial chemotherapeutics by its nature and it has different kinds of mechanisms to become resistant to antibiotics. Therefore, strains that would be extremely resistant to almost all classes of antibiotics are likely to occur, mostly in the hospital environment.

Materials and methods: This study included a sample of 438 isolates of *Pseudomonas species* from 275 individuals, which were isolated in a pure culture at the Department of Microbiology with the Institute for Public Health of the Sarajevo Canton in 2019. After applying standard microbiological methods for identification of *Pseudomonas species*, antimicrobial sensitivity/resistance testing of the isolates was carried out.

Results: The obtained results of antimicrobial sensitivity/resistance testing show that, out of a total of 404 isolates tested for ciprofloxacin (ofloxacin), 48 (11.9%) isolates were resistant and 356 (88.1%) sensitive; out of a total of 423 isolates tested for gentamicin, 28 (6.6%) isolates were resistant and 395 (93.4%) sensitive; out of a total of 430 isolates tested for chloramphenicol, 396 (92.1%) isolates were resistant and 34 (7.9%) sensitive; out of a total of 430 isolates tested for piperacillin/tazobactam, 33 (7.7%) isolates were resistant and 397 (92.3%) sensitive; all 3 (100%) isolates tested for amikacin were sensitive; out of a total of 422 isolates tested for imipenem, 19 (4.5%) isolates were resistant and 403 (95.5%) sensitive; out of a total of 430 isolates tested for cefepime, 130 (30.2%) isolates were resistant, 297 (69.1%) sensitive and 3 (0.7%) I; out of a total of 430 isolates tested for ceftazidime, 122 (28.4%) were resistant, 304 (70.7%) sensitive and 4 (0.9%) I.

Conclusions: In our study, *Pseudomonas species* showed sensitivity to imipenem in 95.5% of isolates, piperacillin/tazobactam 92.3%, gentamicin 93.4%, ciprofloxacin (ofloxacin) 88.1%, ceftazidime 70.7% and cefepime 69.1%; it showed the highest resistance to chloramphenicol in 92.1% of isolates, resistance to cefepime 30.2% and resistance to ceftazidime 28.4%. In order to reduce bacterial resistance to antibiotics, it is necessary to follow specific measures when prescribing antibiotics; it is necessary to educate and raise awareness about the rational use of antibiotics, as well as to regularly monitor the resistance of the most prevalent causal agents of outpatient infections at both the local and global levels.

Key words: *Pseudomonas*, antimicrobial resistance, multiple resistance, outpatients.

1. Introduction

The *Pseudomonas* genus is one of the most complex bacterial genera and it also belongs to Gram-negative bacteria with the largest number of different species, which keeps growing year after year. There are currently 144 recognized species of the *Pseudomonas* genus, the most important representative of which belongs to the fluorescent group - *Pseudomonas aeruginosa* (1). This pathogen has been renamed several times throughout history, based on specific green-blue coloration that occurred in the process of cultivating. The oldest data dates back to 1850, when Sédillot no-

ticed a change of color on a surgical wound bandage, which he brought into connection with the presence of an infectious microorganism. Blue pigment was extracted for the first time in 1860 and, two years later, this pigment was brought into connection with a rod-shaped organism. Carle Gessard is the first person who managed to isolate *Pseudomonas aeruginosa* in a pure culture, after he noticed some blue-green pus on the skin wounds of two soldiers. This happened in 1882, when he published his study "On the blue and green coloration of bandages" (2). Thanks to advancements in molecular medicine and more detailed studies of bacterial genomes, many bacteria have been classified into other genera. The *Pseudomonas* genus was divided into five groups designated as the rRNA groups I-V. Bacteria from the rRNA groups II-V have been recently transferred to other genera such as: *Burkholderia*, *Ralstonia*, *Acidovorax* and *Brevundimonas*. The rRNA group I is the only group whose species remained in the *Pseudomonas* genus and they were divided into eight groups: *Pseudomonas aeruginosa*, *Pseudomonas chlororaphis*, *Pseudomonas fluorescens*, *Pseudomonas pertucinogena*, *Pseudomonas putida*, *Pseudomonas stutzeri*, *Pseudomonas syringae* and *incertae sedis*. Among the abovementioned, *Pseudomonas aeruginosa* is most frequently isolated from clinical samples (3).

Bacteria of the *Pseudomonas* genus are asporogenous and aerobic Gram-negative bacilli; on the Gram-stained microscope slide, they look like short and straight rods that are 1.5-5 micrometers long and 0.5-1 micrometer wide and they appear separately, in pairs, chains or piled next to each other. Pseudomonads are motile bacteria with one or more polar flagella, some of the species possess fimbriae, and they are all widely distributed in soil, water, plants and animals, with predispositions towards a moist environment. These ubiquitous bacteria are able to adapt to different kinds of living conditions and they can be found in a variety of environments. Certain species can reproduce at 4°C and up to 42°C, but most of them are mesophilic with an optimum temperature for growth and development ranging between 30 and 37°C. One of the features of pseudomonads is the ability to create the following water-soluble pigments: blue pigment - pyocyanin, yellow pigment - pyoverdine, red pigment - pyorubin and black pigment - pyomelanin. *Pseudomonas aeruginosa* is medically the most important species within the *Pseudomonas* genus, given the fact that it has the invasive ability and numerous factors of virulence and toxicity. Infections caused by *P. aeruginosa* are mostly opportunistic infections in immunocompromised patients, which may affect all organic systems. These infections tend to occur with hospitalization and health care quite frequently, with *P. aeruginosa* being one of the most important causal agents of hospital infections. Compared to enterobacteria, *P. aeruginosa* is a bacterium that is resistant to antimicrobial chemotherapeutics by its nature and it has different kinds of mechanisms to become resistant to antibiotics. Therefore, strains that would be extremely resistant to almost all classes of antibiotics are likely to occur, mostly in the hospital environment (4). *P. aeruginosa* easily becomes resistant to antibiotics through many mechanisms. Development of resistance to beta-lactam antibiotics *in vivo* during therapeutic treatment is often a result of depression of chromosomal beta-lactamase, so some antibiotics are potent inducers of such enzymes and they are able to select a sub-population that is also resistant to other antibiotics from the same group. Pseudomonad accumulates many genetic mutations with phenotypic manifestations through one of the already mentioned mechanisms, and it may also acquire many other enzymes through the horizontal transfer of genetic material (conjugation and transduction), such as extended spectrum beta-lactamases, metallo-beta-lactamases (*carbapenemases*) etc. (4, 5).

2. Materials and methods

This study included a sample of 438 isolates of *Pseudomonas species* from 275 individuals, which were isolated in a pure culture at the Department of Microbiology with the Institute for Public Health of the Sarajevo Canton in 2019. After applying standard microbiological methods for identification of *Pseudomonas species*, antimicrobial sensitivity/resistance testing of the isolates was carried out applying an antibiogram. Antibiogram is a test used to examine sensitivity or resistance of a given microorganism to certain antibiotics.

The disc-diffusion method was applied. The reading reveals three different categories of sensitivity: S (sensitive) - there is a high probability that therapy will be successful after administering an antibiotic, I (intermediate) - therapy is likely to be successful if a maximal concentration of an antibiotic is administered, R (resistant) - therapy will be unsuccessful even if a maximal concentration of an antibiotic is administered.

3. Results

The obtained results of antimicrobial sensitivity/resistance testing show that, out of a total of 404 isolates tested for ciprofloxacin (ofloxacin), 48 (11.9%) isolates were resistant and 356 (88.1%) sensitive; out of a total of 423 isolates tested for gentamicin, 28 (6.6%) isolates were resistant and 395 (93.4%) sensitive; out of a total of 430 isolates tested for chloramphenicol, 396 (92.1%) isolates were resistant and 34 (7.9%) sensitive; out of a total of 430 isolates tested for piperacillin/tazobactam, 33 (7.7%) isolates were resistant and 397 (92.3%) sensitive; all 3 (100%) isolates tested for amikacin were sensitive; out of a total of 422 isolates tested for imipenem, 19 (4.5%) isolates were resistant and 403 (95.5%) sensitive; out of a total of 430 isolates tested for cefepime, 130 (30.2%) isolates were resistant, 297 (69.1%) sensitive and 3 (0.7%) I; out of a total of 430 isolates tested for ceftazidime, 122 (28.4%) were resistant, 304 (70.7%) sensitive and 4 (0.9%) I; 1 (100%) isolate tested for colistin sulfate was S; all 3 (100%) isolates tested for polymyxin B were S; all 4 (100%) isolates tested for meropenem were S.

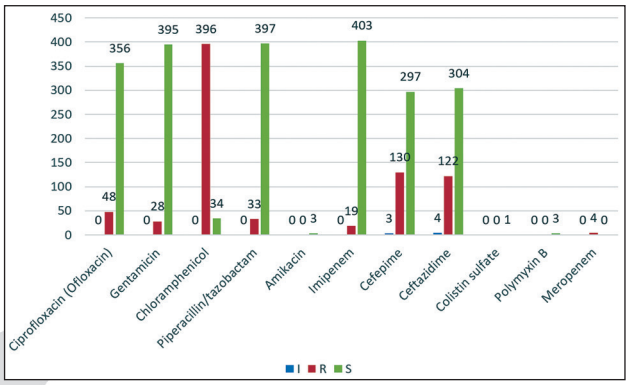

Chart 1. Ratio between results of antimicrobial sensitivity/resistance of Pseudomonas spp. isolates

4. Discussion

At a meeting in Geneva in January 2017, a group of experts from the World Health Organization (WHO) decided to compile a list of pathogens for which it is a priority to discover new antibiotics as soon as possible, based on sensitivity/resistance of the world's most prevalent microorganisms. The list consists of three priority groups: a critical group, a high-risk group and a medium-risk group. The critical group consists of three pathogens that are *carbapenem*-resistant, listed in the following order: *Acinetobacter baumannii* is ranked the first, *Pseudomonas aeruginosa* is ranked the second and *Enterobacteriaceae* are ranked the third. *Pseudomonas aeruginosa* is ranked the second in the critical group of bacteria, which represents an alert to discover new antibiotics against this pathogen as soon as possible (6).

In our study, the *Pseudomonas* genus isolates showed the highest resistance to chloramphenicol, cefepime and ceftazidime. *Pseudomonas species*

Table 1. Results of antimicrobial sensitivity/resistance of Pseudomonas species isolates

Antibiotic	I %	R %	S %	Total (100%)
Ciprofloxacin (Ofloxacin)	0	48 (11,9)	356 (88,1)	404
Gentamicin	0	28 (6,6)	395 (93,4)	423
Chloramphenicol	0	396 (92,1)	34 (7,9)	430
Piperacillin/tazobactam	0	33 (7,7)	397 (92,3)	430
Amikacin	0	0	3 (100)	3
Imipenem	0	19 (4,5)	403 (95,5)	422
Cefepime	3 (0,7)	130 (30,2)	297 (69,1)	430
Ceftazidime	4	122 (28,4)	304 (70,7)	430
Colistin sulfate	0	0	1 (100)	1
Polymyxin B	0	0	3 (100)	3
Meropenem	0	4 (100)	0	4

showed resistance to ciprofloxacin (ofloxacin) in 11.9% of isolates, gentamicin 6.6%, chloramphenicol 92.1% and piperacillin/tazobactam 7.7%; all 3 (100%) isolates tested for amikacin were sensitive; 4.5% of isolates were resistant to imipenem, 30.2% of isolates were resistant to cefepime while 0.7% were I, 28.4% of isolates were resistant to ceftazidime while 0.9% were I; 1 (100%) isolate tested for colistin sulfate was S, all 3 (100%) isolates tested for polymyxin B were S and all 4 (100%) isolates tested for meropenem were S. In a study in India, 40% of isolates showed resistance to gentamicin, while 39% showed resistance to ciprofloxacin (7). In a study in Malaysia, resistance to cefepime was 37.03% (8). In our study, sensitivity to imipenem was 95.5%. In the study in Malaysia, *Pseudomonas aeruginosa*'s sensitivity to imipenem was 81.49% (8). There was 69.1% sensitivity to cefepime as a fourth-generation cephalosporin, 93.4% to gentamicin from the group of aminoglycosides and 88.1% to ciprofloxacin from the group of fluoroquinolones.

Of all Gram-negative bacteria, *Pseudomonas aeruginosa* is the leading pathogen that causes infections with a high mortality rate, which are narrowly connected to the constant growth in antimicrobial resistance to the majority of antibiotics (9). Multiple resistance grows year after year and possible causes of the constant growth are topics of many papers across the world. *Pseudomonas aeruginosa* is naturally resistant to many antibiotics; combined with different kinds of risk factors, such resistance makes this pathogen quite challenging in terms of total eradication from an organism. When it comes to beta-lactam antibiotics, *Pseudomonas aeruginosa* has the ability to produce serine beta-lactamase (10). Aside from being an enzyme producer, this pathogen possesses a cell membrane that can be semipermeable or impermeable against aminoglycosides, quinolones and beta-lactam antibiotics, depending on a strain. Such feature of the cell membrane originates from the LPS modification, change of proteins within the membrane and inactivation of the enzyme complex (11). Over the last few years, there has been a major growth in resistance to carbapenems that have been used for a long time, which can only be replaced by polymyxins, antibiotics that represent the last line of defense (12). The fact that resistance to polymyxins is often registered in the world is concerning as well, which leaves no other options in the treatment of infections caused by *Pseudomonas aeruginosa*. The most frequent mechanism of the acquired resistance to polymyxins is a change in the structure of lipopolysaccharides of the outer cell membrane (13). In order to reduce bacterial resistance to antibiotics, it is necessary to follow specific measures when prescribing antibiotics in everyday practice, including the rational use of antibiotics, cycling and rotation of antimicrobial medicines prescribed. It is also necessary to educate and raise awareness of the entire population that antibiotics should not be used without a justifiable reason.

5. Conclusions

Pseudomonas species showed sensitivity to imipenem in 95.5% of isolates in our study.

Sensitivity to piperacillin/tazobactam in 92.3% of isolates, gentamicin 93.4%, ciprofloxacin (ofloxacin) 88.1%, ceftazidime 70.7% and cefepime 69.1%.

It showed the highest resistance to chloramphenicol in 92.1% of isolates.

Resistance to cefepime in 30.2% of isolates and ceftazidime 28.4%.

In order to reduce bacterial resistance to antibiotics, it is necessary to follow specific measures when prescribing antibiotics.

It is necessary to educate and raise awareness about the rational use of antibiotics, as well as to regularly monitor the resistance of the most prevalent causal agents of outpatient infections at both the local and global levels.

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Bioethics in online epidemiological research: an integrative review

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Abstract

Introduction: There is an increasing use of online data collection for scientific research worldwide, yet the privacy, confidentiality and safety of the research participants are at risk at the time the data is transmitted to outsiders, so the researcher must consider the bioethical precepts for research involving human beings. The aim of this review was to describe and analyse the range of publications with epidemiological approaches that use an online platform for research and their respective ethical aspects.

Methods: In October 2017, an integrative review of electronic databases was carried out using descriptors.

Results: Independent researchers applied the inclusion and exclusion criteria and found 33 articles organized according to year, author, country, epidemiological studies, rate or number of participation, research participants and bioethical aspects. Online epidemiological surveys were mostly carried out in the United States (36.3%) using descriptive and exploratory approaches (78.7%). The online Survey MonKey platform was reported in 81.8% of the surveys, with evaluations and updates of practices of health professionals, especially among nurses and medical specialists related to medical societies, public programs or universities. Thirty percent of the studies had a higher response rate than 50%. The three categories described that involved Bioethical aspects were: a) types of anonymity (institutional and participants) and voluntariness; b) types of approvals and consents (implicit, explicit and verbal); c) without the mention of ethical aspects.

Conclusions: Data collection for epidemiological surveys using online platforms might enable multicenter studies. The offer of prizes to participants appear to increase the participation rate while the not mentioning of bioethical aspects reduce the participation. The voluntariness in these surveys may be related to confidentiality when there is a fear of responding to studies that may lead to stigma and prejudice.

Key words: Bioethics, Online research, review

Introduction

The internet is a social phenomenon and a field for research. Different epidemiological, logistical and ethical aspects would be considered depending on the role of the internet in the research project and on the conceptualization given by the researcher. Many ethical and methodological concerns arise and therefore, internet research requires new models of evaluation and ethical consideration. In this study, the internet was employed as a field of research for the collection of data or information through online platforms [1].

In this context, bioethics in research looks again towards the relationship between the researcher and the subject of research who participate voluntarily in the research, in order to protect the participant and give priority to its welfare ahead the interests of science and society [2].

The use of online data collection for research is increasing worldwide. The benefits are the saving of time and travel expenses, the increased security, and the exchange of text, audio and visual information as well as live interactions using Skype, if required, between the researcher and the participant. However, there are restrictions to this type of methodology, such as the absence and/or access restrictions to internet resources, and the capabilities of both participants and researchers to use the internet and the software [3, 4].

Health aspects, when studied at the population level, are objects of epidemiology analysis that provide essential information for health professionals, policymakers, and social analysts. Epidemiological studies reveal the frequency of a disease or the

effects of the different interventions for disease control, aid the research of disease causes and the analysis of social factors that constrain health and disease in large-scale population studies [5].

Growing evidence confirm that internet surveys can yield representative data especially in the case of some hard-to-reach populations, although they may also under-represent some populations [6].

The privacy, confidentiality, and safety of research participants are at risk at the time the data are transmitted electronically to outsiders [5]. Confidentiality can be ensured through processes similar to those used with traditional methods, such as password protection of the database and granting access only to certain members of the research team [3].

In this sense, online questionnaires such as Google Forms, Bristol Online Survey and Survey Monkey provide the opportunity to develop online surveys with a comprehensive freedom to customize multiple-choice fields, text boxes, videos, figures, and tools for analyzing results.

A rapid Internet search highlights the advantages of the platforms by comparing the characteristics of the questionnaires, the possibilities to send and follow the questionnaires and the answers. In addition, there are services available for free, such as Google Forms, or the possibility to select the free trials of the search tools Survey Monkey and Bristrol Online Survey, limited to 30 days.

Considering the information available in the online platforms, a considerable gap is evidenced in the importance given to the research participant. In this context, the researcher has the responsibility of attending to the bioethical precepts for research involving human beings, and clarifying the principles of international bioethics, such as the following principles of the Belmont Resolution: a) beneficence; b) autonomy; c) justice and; d) non-maleficence [7].

In view of this scenario, the following questions emerged to guide the study using online questionnaire platforms for epidemiological research involving human beings: Which are the most used online questionnaire platforms? What are the goals of these surveys? Which are the most common epidemiological studies: analytical or descriptive? What is the average participation rate or the number of participants? Which countries and languages use these platforms the most? Who are the participants who most respond to epidemiological research on platforms of online questionnaires? What bioethical aspects are present in the epidemiological surveys using online questionnaire platforms? If so, in which way?

Considering that scientific research aims at expressing the current social practices, as well as the information and communication technologies present in the daily life of people and researchers, these questions motivated the search for knowledge in publications of health sciences databases, in order to increase the understanding on the uses of online research platforms for data collection in epidemiological surveys and the presence of bioethical aspects of health research involving human beings.

Methods

The present integrative literature review allowed the synthesis of several studies and the analysis of the scientific knowledge in publications that used online questionnaire platforms to collect epidemiological data and their respective bioethical aspects.

As proposed by Mendes et al. [8], the construction of this integrative review followed the following stages:

1) Identification of the subject and selection of hypothesis and research questions for the elaboration of an integrative review;
2) Establishment of inclusion and exclusion criteria of studies for the literature search;
3) Definition of the information to be extracted for the selected studies/ study categorization;
4) Evaluation of the studies included in the integrative review; and
5) Categorization and descriptive interpretation of results.

For the selection of references, the following electronic databases were considered: Public Medline (PubMed), Web of Science, Scopus and Cochrane Library. It should be noted that each of these databases contains diverse indexed databases, for example, PubMed comprises the MEDLINE database, the Life Sciences journals and online books.

After defining the research databases, we assessed the descriptors controlled and indexed in the terms MeSH (Medical Subject Headings Section) and DeCS (Descriptors in Health Sciences). Then,

two double-blind researchers searched for references using the Boolean operator "AND", keeping the first term "health" and replacing the synonyms "survey", "search", and "research"; and the online questionnaire platforms names: "Google Forms", "Survey Monkey" and "Bristol Online".

The methodological procedures of search, selection and analysis of articles were carried out by two independent researchers, who compared their selections. In this way, the results between researchers were calibrated with 100% accuracy. The same procedure was followed for the article pre-selection until the selection of the final sample of articles. The flowchart of this methodology is described in Figure 1.

For the selection of articles, the following inclusion criteria were adopted: 1) original articles with exclusively epidemiological approach with data collection on humans beings, answered only through one of the following online questionnaire platforms: Google Forms, Survey Monkey or Bristol Online Survey; 2) articles full-text available online, published in Portuguese, English and Spanish; 3) articles published from 2013 to September 2017 and indexed in the selected databases.

The exclusion criteria were studies recognized as secondary research (literature revision of either systematic or integrative narratives), Annals of congress, editorials, letters responses, dissertations and theses and articles with mixed research methods and in qualitative health, research involving animals, research using unidentified online platforms and the filling with online research tools or by the researcher, in the absence of the participant.

In order to identify the studies, we carried out a careful reading of the titles, abstracts and keywords, and in some cases, of the article full text retrieved by the search strategy, for further verification of their adequacy to the inclusion and exclusion criteria [8]; and when this information was not found, the article was deleted.

The results were organized according to the identifying information of the articles (year of publication, name of the journal, title and authors) and of the variables to facilitate the analysis by answering the research questions:

a) Types of epidemiological studies (descriptive or analytical): descriptive studies describe the frequency, natural history and possible determinants of a condition [6]. These hypotheses can be tested through more rigorous research, such as analytical studies or randomized controlled trials. Analytical studies allow the analysis of potential causal associations [5].
b) Research participants: people who answered online surveys;
c) Participation rate or number of participants: percentage of responses to surveys or number of participants when the survey is available on the web and the participants responded digitally;
d) Absence or presence of bioethical aspects: part(s) of articles indicating bioethical characteristic (s) according to the international principles of autonomy, beneficence, non-maleficence, and justice [7], for the analysis of records of bioethical characteristics in health research.

Therefore, in this integrative review, we outlined a map of the scientific production on the use of online questionnaire platforms for data collection in epidemiological research, analysing and discussing the data from the perspective of the bioethical aspects of epidemiological research in health involving human beings.

Results

We identified 626 articles. After reading the titles, abstracts or complete articles, we verified that 268 articles were repeated in different databases, and 315 articles did not meet the inclusion criteria and were excluded, along with 10 articles that, although they were within the established criteria for inclusion, their full texts were not available (Figure 1).

The final sample of this review consisted of 33 articles (Table 1): three published in 2013, seven in 2014, 14 in 2015, five in 2016 and four in 2017. The articles were published in 33 different journals, being 29 in English, three in Portuguese and one in Spanish. Twenty six articles used a descriptive epidemiological approach (78.7%) while in seven articles the epidemiological approach was analytical (21.2%).

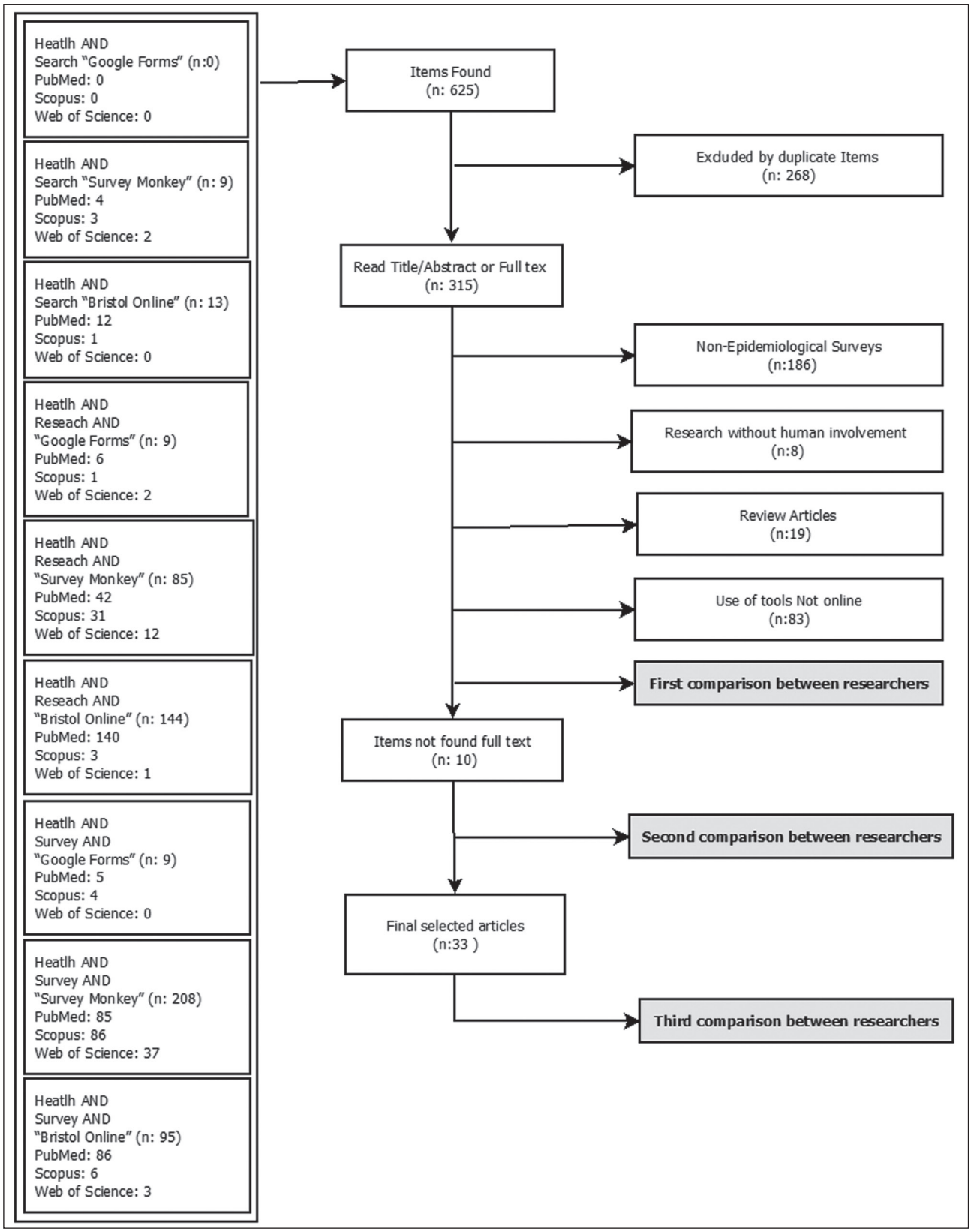

Figure 1. Search result of electronic databases according to the inclusion and exclusion criteria of article selection by independent researchers in 2017

Table 1. Distribution of articles according to characteristics and mention of ethical aspects in epidemiological research, 2018

Author(s)	Online Platforms	Country	Research participants	Participation Rate	Presence of ethical aspect (s)
Deligianni E, Corkery JM, Schifano F, Lione LA.	Bristol Online	UK	University educated students	83%	"The study was approved by the University of Hertfordshire's Health and Human Sciences Research Institute Ethics Committee. Informed consent was assumed by individuals agreeing to proceed with the survey. The survey was entirely anonymous" (Deligianni et al., 2017).
Javadian S, Stigler-Granados P, Curtis C, Thompson F, Huber L, Novotny TE.	Survey Monkey	USA	Representing the Framework Convention Alliance (FCA).	28%	"The email listserv of FCA members was provided to CBPP by the FCA Secretariat in Washington, DC. […] The online survey was administered according to FCA communication protocols. The study was approved by the Institutional Review Board of San Diego State University. No incentives were offered for participation, and an informed consent statement was provided upon beginning the survey, indicating the voluntary and confidential nature of the study. Information collected was confidential but not anonymous, as we were interested in the types of organizations and membership status of participants. The respondents to this survey provided individual-level responses rather than institutional positions" (Javadian et al., 2015).
Ousey K, Rippon M, Stephenson J.	Survey Monkey	UK	Healthcare professionals working within tissue viability services	31%	"Ethical approval to distribute the survey was received from the School of Human and Health Sciences Research and Ethical Panel at the University of Huddersfield" (Ousey et al., 2016).
Shivaji UN, Ford AC.	Survey Monkey	UK	Primary care physicians	37.1%	"The questionnaire was sent to the email addresses of all 275 primary care physicians in Leeds in May 2013, via the three clinical commissioning groups in the city" (Ousey et al., 2016).
Wright W, Khatri N.	Survey Monkey	USA	Nurses employed across three facilities at a university hospital system in the Midwest.	23%	"The purpose of the study was reviewed with the Director of Nursing for support and consent to proceed. The research study was also reviewed and approved by the University of Missouri Institutional Review Board before data collection".[...] An email was sent to the respondents explaining the purpose of the study and inviting them to participate. Completion of the survey indicated their consent to participate in the study. In addition, participants were informed that the data being collected were voluntary and would be confidential and responses would not be identified individually" (Wright and Khatri, 2015).

Dauw CA, Simeon L, Alruwaily AF, Sanguedolce F, Hollingsworth JM, Roberts WW, Faerber GJ, Wolf JS Jr, Ghani KR.	Survey Monkey	UK	Endourologists worldwide	414 surgeons	"...an anonymous online questionnaire... Respondents were invited to participate through an introductory email from the Endourology Society membership office with a brief description of the survey and a hyperlink of the survey [...] "The survey was deemed exempt from requiring review by the Institutional Review Board at the University of Michigan."" To improve participation, a $200 award was offered to one respondent selected at random" (Dauw et al., 2015).
Baysa SJ, Olen M, Kanter RJ, Fishberger SB.	Survey Monkey	USA	Members of the Pediatric and Adult Congenital Electrophysiology Society (PACES)	n=108	"Don´t mentioned ethical aspects" (Baysa et al., 2016).
Tsapaki V, Rehani MM.	Google Docs	USA	Medical physicist	n=17024	"The regional organizations were asked to distribute it among national member organizations (NMOs) and even to non-IOMP member countries. [...] The response rate at the regional level was very poor as only the USA, the Middle East Federation of Organization of Medical Physics (MEFOMP) and the South East Asian Federation of Organizations for Medical Physics (SEAFOMP) could provide some data". " It was decided to reach out to official contact points (Secretary or President) in national member countries. Repeated reminders were then sent between mid-April and mid-July 2013. Further, the Secretary-General of IOMP used his personal contacts in many countries to increase response. Both developed and developing countries were included in the survey" (Tsapaki and Rehani, 2015).
Candler T, Mahmoud O, Edge J, Hamilton-Shield J.	Survey Monkey	UK	280 members of the Association of Children's Diabetes Clinicians	87 diabetes professionals	"Permission for distribution was kindly agreed and subsequently circulated by the chair of the Association" (Candler et al., 2017).
Buhrow, Suzanne Morse DHA, RN; Buhrow, Jack A. DDS, MS	Survey Monkey	USA	27 four-year oral and maxillofacial surgery residency program directors	74%	"The program directors' emails were obtained from the list of accredited OMFS residency programs for academic year 2011-2012 published by the American Association of Oral and Maxillofacial Surgeons.[...] The purpose of the survey and voluntary participation was described in the introductory letter to potential participants". "The identity of respondents and sponsoring institutions remained anonymous" (Buhrow and Buhrow, 2016).

Johnson SJ, Alford C, Verster JC, Stewart K.	Survey Monkey	UK	University student	n=1873	"UK university student unions (N = 139) were contacted via email and asked if they would be willing to advertise the AMED student survey via their social media platforms. In total 30% of student unions, including institutions from each country (England, Wales, Scotland, and Northern Ireland) responded and agreed to disseminate a short summary of the surveys content and web link. Prior to commencing the study ethical approval was granted by the University of the West of England ethics committee. On opening the link participants were informed of the purpose and content of the survey, and were told that participation was anonymous and voluntary. Upon completion of the study, participants were offered the opportunity to be entered into a prize draw (1 × £500, 10 × £50). Entrance to the survey required participants to provide an email address. To ensure anonymity, the email address provided was not linked to the participant's survey responses" (Johnson et al., 2016).
O'Reilly AC, Walshe M.	Survey Monkey	UK	Language therapists	322	Consent was implied by the participants when they completed the survey. The survey was anonymous. However, if participants identified themselves during the course of the survey, the data were anonymized and were not reported in a way that identified the participant. Data protection legislation was adhered to throughout the course of the study" (Oreilly and Walshe, 2015).
Al-Nouri O, Sinacore J, Halandras P, Hershberger R.	Survey Monkey	USA	Members of the society of vascular surgery	5.4%	"Don´t mentioned ethical aspects" (Al-Nouri, 2015).
Javadian P; Wendelken J; Quiroz LH; Shobieri AS.	Survey Monkey	USA	Surgeons	n= 79	"IRB approval was obtained from the institutional review board before conducting this research" (Javadian et al., 2015).
Stewart A, Ganguli A, FitzGerald R, Pirmohamed M.	Survey Monkey	UK	Anticoagulation clinics	43%	"Local Research Ethics Committee approval was not sought as this was a survey of current clinical practice. Verbal consent from healthcare professionals was obtained via telephone for AS to make contact via their NHS email with a survey link" (Stewart et al., 2015).
Embun R, Martínez Hernández N, Call S, de Olaiz Navarro B, Zabaleta J, Ramos R, Galbis J, Moreno N.	Survey Monkey	Spain	Departments from the public and state-assisted national health system and 315 thoracic surgeons	56.5%	"The list of e-mail addresses was provided by the Technical Secretary of the SECT to R.E., coordinator of the Scientific Committee of the Society" (Embun et al., 2017).

Gesser-Edelsburg A, Shir-Raz Y, Hayek S, Sassoni-Bar Lev O.	Google Docs	Israel	Israeli public	n= 327	"This research has been approved by the University of Haifa Faculty of Social Welfare and Health Sciences Ethics Committee for Human Research" (Gesser-Edelsburg et al., 2015).
Kamran Sattar, Sue Roff and Sultan Ayoub Meo	Bristol Online	Saudi Arabia	Students of College of Medicine, King Saud University.	52%	"An anonymous, self-administered [...] bilingual inventory [...] was used. The survey included consent of the participants". "The Institutional Review Board of College of Medicine, King Saud University approved the study" (Sattar et al., 2016).
Cunningham J, Horsley J, Patel D, Tunbridge A, Lalloo DG.	Survey Monkey	Spain	Foreign and Commonwealth Office employees on long-term placement.	56,5%	"This survey was performed as a service review against existing gold standard recommendations and ethical approval was therefore not required". (Cunningham et al., 2014).
Gurunluoglu R, Gurunluoglu A, Williams SA, Tebockhorst S.	Survey Monkey	USA	American Society of Plastic Surgeons	21.70%	"The survey Current trends in breast reconstruction was presented to the Compliance and Regulatory Department at the University of Colorado Health Sciences, and project approval was obtained" (Gurunluoglu et al., 2013).
Duarte F, Serranheir F.	Survey Monkey	Portugal	Dental hygienists	61.20%	"The study was approved by the University of Évora, guaranteeing from the ethical and deontological point of view all the recommendations of the Helsinki Committee, namely the confidentiality of data"(Duarte and Serranheira, 2015).
Ventura CAA, Mendes IAC, Wilson LL, Godoy S, Tamí-Maury I, Zárate-Grajales R, Salas-Segura S.	Survey Monkey	Brazil	Deans, course coordinators and nursing departments of 80 HEI in Brazil	n=222	"After receiving authorization from the Research Ethics Committee at the University of São Paulo at Ribeirão Preto College of Nursing (Opinion 1135/2010) [...] Ethical guidelines were followed, in compliance with National Health Council Resolution 196/96, and the entire process was online and voluntary, in accordance with each subject's interest, availability and time" (Ventura et al., 2014).
Hanson M.	Survey Monkey	Brazil	Human resource officers at each institution included in the population were surveyed.	27.20%	"Don´t mentioned ethical aspects" (Hanson, 2013).

Derby-Davis MJ	Survey Monkey	USA	Participants included a convenience sample of nursing faculty teaching in baccalaureate and graduate nursing programs in Florida	n=134	"The researcher protected the participants in the proposed study by adhering to ethical and legal guidelines. All policies for protection of human subjects mandated by the university institutional review board were followed. The cover letter indicated that participation in the study was voluntary and that participants had the right to withdraw from the study without incurring adverse consequences. By logging on to the Survey Monkey Web site and initiating the survey process implied consent; therefore, a separate consent form was not required. The researcher did not collect any personal identifiable information from the participants. The answers to the survey questions were directly imported into the Survey Monkey database file without showing the participant's name or e-mail address. Upon completion of the survey, the data were stored on the secure server by Survey Monkey until it was downloaded on the researcher's personal computer, which was password protected" (Derby-Davis, 2014).
Errett NA, Bowman C, Barnett DJ, Resnick BA, Frattaroli S, Rutkow L.	Survey Monkey	USA	The point(s) of contact for each Urban Area Security Initiative.	77.80%	"The Johns Hopkins Bloomberg School of Public Health Institutional Review Board reviewed this study and determined it to be not human subject research" (Errett et al., 2014).
Janoo J, Hashmi M, Seybold DJ, Shapiro R, Calhoun BC, Bush SH.	Survey Monkey	USA	All program directors of Obstetrics and Gynecology programs in the United States of America	28%	"Authors mailed the survey with a letterhead cover page introducing the research and clarifying the voluntary nature of the questionnaire. [...]The completed survey was then accessible to the investigators via a unique login password account with Survey Monkey created specifically for this project" (Janoo et al., 2015).
Putze GB, Acosta JD, Castro SM, Duarte JIH, Lozano MB, Sánchez MAJ, García CF, Rodríguez ME, Sosa AJ.	Google Docs	Spain	Doctors and nurses of the Spanish emergency services.	n=364	"Including in it the link to answer it, completely anonymously, when the respondent cannot be identified ... The request to participate was made between March 24 and April 10, 2011. The recipients' emails were obtained from members of the Toxicology Group of the Spanish Society of Emergency and Emergency Medicine (SEMES) and the partners of SEMES-Canarias, SEMES-Andalucía, SEMES-Aragón, SEMES-Euskadi, SEMES-Catalonia and SEMES-Madrid. It was also available on the SEMES website, where emergency and emergency professionals were invited to participate. The universe of participants, based on SEMES partners" (Burillo et al., 2015).

Schallhorn J, Haug SJ, Yoon MK, Porco T, Seiff SR, McCulley TJ.	Survey Monkey	USA	The members and affiliates of the American Society of Ophthalmic Plastic and Reconstructive Surgery, the North American Neuro-Ophthalmology Society, and the American College of Rheumatology	n= 1074	"No personal or institutional data were collected. Institutional review board approval was obtained before the start of the study" (Schallhorn et al., 2013).
Dushianthan A, Cusack R , Chee N, Dunn JO, Grocott MP.	Survey Monkey	UK	At intensive care physicians managing adult patients (more than 18 years of age)	11%	"Ethical approval was obtained from the University of Southampton Ethics and Research Committee" (Dushianthan et al., 2014).
Hassidim A, Korach T, Shreberk-Hassidim R, Thomaidou E, Uzefovsky F, Ayal S, Ariely D,	Google Docs	Israel	Medical and paramedical personal.	n= 299	"This study was granted an Institutional Review Board waiver by the Israeli Defense Force IRB, as no clinical personal subject data were collected or used" (Hassidim et al., 2017).
Keenan M, Greer AE.	Survey Monkey	USA	University faculty members at a northeastern, liberal arts university.	30%	"Survey respondents were recruited through global e-mails describing the study and requesting voluntary participation. Informed consent was obtained from all respondents. All study procedures were approved by the Sacred Heart University Institutional Review Board" (Keenan and Greer, 2015).
Halila GC, Junior EH, Otuki MF, Correr CJ.	Survey Monkey	Brazil	All pharmacists registered in Parana State, Brazil,	8.50%	"Ethical approval for the study was obtained from the State University of Ponta Grossa Ethical Committee. [...]From the moment the participant read the consent form and clicked on the option to continue the consent was considered as accepted. If there was disagreement with the content of the term, the participant could click on the exit option" (Halila et al., 2015).

Marks A, Wilson V, Crisp J.	Survey Monkey	Australia	Parents (66) of children with type 1 diabetes attending an Australian primary school	n=66	"Electronic links were then available for the online anonymous questionnaire if parents chose to participate. [...] A amostragem voluntária, intencional, voluntária foi utilizada para este estudo" (Marks et al., 2014).

Source: research data, 2018.

The average rate of participation in surveys, using online questionnaire platforms, was 41.1%. Regarding the number of answers to the forms of research available on the web, the minimum was 66 and the maximum was 17024.

Thirty percent of the studies identified as descriptive had a higher response rate than 50% and aimed at evaluating the practice of students and health professionals. In this context, the health professionals were the majority (66.6%) of the research participants, followed by university students (15.0%), while others represented 18.1%. Regarding the amplitude of the studies, 39.3% covered more than one country, while 18.1% covered more than one continent.

Survey Monkey online questionnaire platform was featured, used in 81.81% of the data collections for research, followed by Google Docs (12.1%) and Bristol Online (6.06%).

The United States of America stood out as the country that most used the platforms of online questionnaires for data collection (36.3%) followed by the United Kingdom (30.30%), Brazil, Portugal and Spain, which had the same index (9.09%), while Saudi Arabia and Australia represented 3.03% of the studies evaluated.

Regarding the Bioethics aspects of the articles: 39.3% of the studies registered the approval by the Research Ethics Committee; 33.3% articles mentioned the anonymity of the research participants, while only 6.06% of articles cited institutional anonymity. Non-anonymous confidentiality was recorded in 3.03% of the articles, anonymous confidentiality in 9.09%, while 6.06% did not make any mention to confidentiality.

Also about Bioethics aspects, 33.3% of the articles had the consent of the participant, being 9.09% implicit and 3.03% reported as verbal consent, by telephone. Voluntary data collection accounted for 24.2%, while the offer of draws for prizes to participants was registered in 6.06% of the articles and the same percentage was found for the records on the protection of the data storage and freedom of the participants to withdraw from research without any consequence.

Discussion

The results of this integrative review evidenced that the use of online questionnaire platforms for data collection on epidemiological research, has been increasingly adopted in organizations with the aim of bringing agility to either academic or institutional research.

Thereafter, we discussed the results of the review, which were based on online epidemiological surveys, mostly carried out in the United States and the United Kingdom, using descriptive and exploratory approaches. These results usually presented bioethical aspects of the research which were also the targets of this discussion and concluded about evaluations and updates of healthcare practices of health professionals, in particular nurses and medical specialists related to medical societies, public programs or universities (Figure 2).

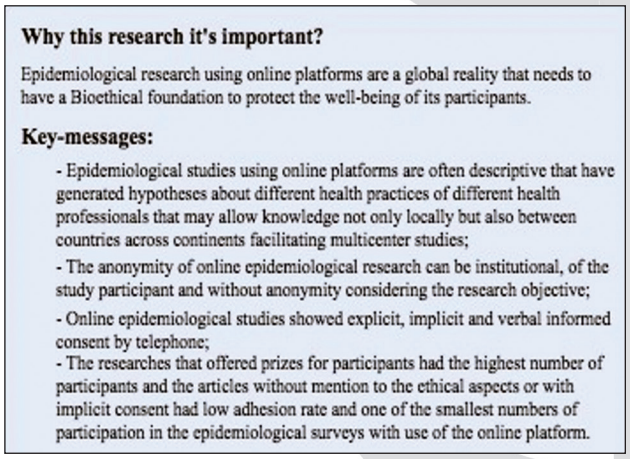

Figure 2. Bioethical aspects of the research

Online questionnaire platforms for epidemiological data collection

Among the online research tools, Survey Monkey stands out as one of the most used, probably because of the time of existence associated with several advantages. The platform offers the possibility of a basic, free plan, with restrictions to some important items, such as a limited number of questions and answers.

Considering the options of plans paid annually, with different prices for each country, the platform does not impose restrictions to questions and answers and also offers the option of numerous functionalities, such as the data export to statistical programs like the Software IBM SPSS Statistics, which reduces the possibility of errors in the transcription of data, expands the possibilities of data analysis and externalization of the information of statistical analysis [9]. Although the Bristol Online tool has similar characteristics to Survey Monkey, the platform offers fee exemption only during the first 30 days of use. Therefore, its use in this review was limited, represented only by two descriptive surveys conducted in 2016 and 2017.

Researchers from Israel, one of the countries included in the present review, documented that doctors and nurses mainly use the Google Forms tool to collect data for epidemiological studies [10, 11]. It is free alternative tool to Survey Monkey that allows users to collect information easily through a search form. The answers are exported to an online spreadsheet that can be visualized through three different ways: a summary of answers, a separate spreadsheet or exported as a .csv file for the analysis of data in external programs [12].

An experience report has shown that in situations in which the estimates of size-effect cannot be gathered from searches by traditional methods, these can be quickly and easily collected through a simple study using e-mail recruitment and an online questionnaire [11].

In this context, online questionnaire platforms are important resources for collecting data in health research, however, they should contemplate the ethical approval required in internationally renowned documents. Therefore, they should present the explanation of the research purpose followed by Informed Consent Form (TCLE) in their introductory section, by requesting the participant the consent to participate in the research and only after agreeing, the participant can get access to the online form. However, in case of refusal, the participant is redirected to the final page in which there is a thank you message.

Participation rate and online survey participants

The authors of the retrieved articles indicated low response rates, however, it was possible to carry out epidemiological studies considering the population representativeness in the study sample, which was mostly descriptive. Response rates might be low if the research has not been adequately targeted to the studied population who should have access to the internet [9].

Waclawski [9] indicated that alternative methods such as posters, bulletin articles, and even letters to participants might be necessary to increase response rates, as e-mail applications with search forms may not be accessed, harming the sample representativeness. The Council for International Organizations of Medical Sciences, an important international organization, presented clear recommendations regarding the purpose disclosure for which the data are being collected and who (researcher and institution) is collecting or accessing them, since there is no face-to-face contact between participants and researchers [5].

Types of epidemiological approaches to online research

Descriptive studies that generated hypotheses about different health practices performed by different health professionals, especially physicians and nurses were frequently found in this review. Analytical studies assessed the relationship between the health practice knowledge and the demographic characteristics or post-treatment effects.

It is worth noting that descriptive epidemiological studies are observational and portray the disease occurrence or other health-related events in relation to geographic areas, periods and demographic characteristics, such as age, sex, educational level, occupation and socioeconomic conditions. They contribute to generating hypotheses about the factors that potentially determine the observed disease patterns. These hypotheses can then be tested in analytical studies and their results used to verify to which extent the disease patterns are represented by the factors [5].

Countries using online questionnaire platforms for publications

Scientists can send electronic files about the results of their research, to other scientists for collaborative purposes, or to build a centralized information repository on a particular subject [5]. The data collection practices of epidemiological surveys using online platforms, identified in this review, can allow knowledge not only at a local scale but also between countries and continents facilitating a multicenter study [14, 15].

Thus, ethical pluralism emerges in Internet research, emphasizing the importance of recognizing different traditions in the ethical decision making of all nations and cultures. Even with ethical pluralism, the protection of the personal integrity and dignity should be first, highlighting the rights to informed consent, privacy, confidentiality, and anonymity [16].

Bioethical aspects of online research

The results of this integrative review showed the following three categories described in articles that involve Bioethics aspects of health research:

a) types of anonymity and voluntariness;
b) types of consent and approvals;
c) without the mention of ethical aspects.

a) Anonymity and Voluntariness:

Online anonymity can encourage people to discuss sensitive issues or express more of what they feel, experience or do [12]. For example, the study that assessed the sharing violation of credential access between health professionals [10]. Two types of anonymity, institutional and of research participants, were registered in this review [17]. The first type may be from the sponsoring institution or the researchers and the second type of anonymity aims to preserve the identity and maintain the confidentiality of the research participant, thus avoiding interfering with the given answers. One way to achieve confidentiality is to use only unidentifiable data, as the disclosure and improper access to research data may cause physical, psychological, social or economic harm to individuals, couples, families or other social groups or infringe their privacy.

Unlike Walker [3] who found that sending the link to the participants by recognized institutions or individuals can guarantee the anonymity of the participants, since there is an intermediary to endorse the project, in this review some links were disclosed and sometimes sent by medical societies, but one of them did not have a good response rate of the participants.

In addition, the articles included in this study were generally confidential, with or without anonymity [18, 19, 20, 21, 22, 23], depending on the research objective. If anonymity was not required, participants were able to read the clarifications

and enter their email addresses if they wish to participate and be contacted directly [3].

A competent person capable of deliberating and having understood the information disclosed, who accept or reject proposals for participation that affect or may affect him [14] made a voluntary decision based on adequate clarifications about the research and manifest the consent of the research online and therefore avoids any problem of coercion of the participant [3].

In the online research [25, 26], voluntariness is associated with confidentiality when there is a fear of responding to studies that can cause stigmas and prejudices.

b) Approval and Consent:

In 1964, the Declaration of Helsinki incorporated ethical principles for the analysis of academic practices. Later, the bioethics assumed these principles and established the need to create Research Ethics Committees, as well as to advise against the publication of objectionable ethics [27]. Supported by this Declaration and other documents protecting research participants, the Research Ethics Committees were created. Several countries started to demand that research projects were previously evaluated with the aim of contemplating specific contextual aspects, in the light of ethical references accepted at international and national level [28].

The approval records of Ethics Committees were present [29, 30, 31, 32, 33, 34, 35, 36] in most of the epidemiological studies using the online platforms that target these studies. The Committees, linked to universities or health institutions [37, 38], approved the seeking of studies to guarantee the principles of scientific validity and Bioethics.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects and the International Ethical Guidelines for Epidemiological Studies guide researchers using online questionnaire platforms for epidemiological research to use the best techniques to inform the research participant about the consent and identify the participants, as well as to collect data, store them and keep them confidential [5,6].

In some countries such as the United States and the United Kingdom, the informed consent is followed by the payment to research participants [14]. Two articles from the United Kingdom mentioned the offer of draws for prizes to research participants. These surveys had the highest response rates among all surveys evaluated, which it might be due to the possibility of receiving a prize [15, 39].

There were ethical divergences between countries regarding the payment to research participants. The main argument was that paying participants is an inevitable reality of contemporary research and that participants are adequately protected by strong ethical and legal devices. On the other hand, other countries consider that payment is an improper constraint with the potential of significantly impact decision-making processes of poor and vulnerable people [24].

The epidemiological studies included in this review presented [33, 34, 40, 41, 42, 43, 44] the consent informed explicitly, implicitly or verbally by telephone. The explicit consents clarify the research objectives and the participants know the importance of the study. In the case of implied consent, the participants accept to respond to the research form, however, clarifications on the use of the data collected are not clearly stated. Implied consent might be related to the low participation rate and number below or close to the median of surveys included in this review. The informed consent, whether implicit or explicit, must be obtained prior to data collection, and it can be obtained via internet, through clarifications about the purposes and risks of the research, followed by the question that clearly states the participation acceptance or not [3].

c) Without the mention of Bioethical aspects

The scientific articles of this review that did not mention the Bioethical aspects of research involving human beings had a low participation rate and one of the lowest number of participants. These articles addressed the specialized medical conduct and were supported by medical societies [45, 46, 47].

Conclusion

As a result of the present integrative review, we concluded that articles with epidemiological approaches, using online research platforms are a worldwide reality. This practice stands out in the United States and the United Kingdom and in a small proportion in European countries such as

Portugal and Spain, in Latin American countries such as Brazil, and also in Asian countries such as Saudi Arabia and Israel.

Epidemiological surveys, which are generally descriptive and exploratory, were intended to know, compare and evaluate the update of healthcare practices of the professionals, in the same country or between different countries, especially among nurses and medical specialists members or not of medical societies, public programs or universities.

In this way, the practice of collecting data for epidemiological surveys using online platforms can enable the knowledge not only at a local scale, but also between countries and between continents. Therefore, ethical pluralism and the facility of multicenter study emerge in Internet research.

The three categories described in the articles that involve bioethical aspects of health research are: a) types of anonymity and voluntariness; b) types of consent and approvals; c) without the mention of ethical aspects. The research that offered draws for prizes to participants had the largest number of participants and the articles with the implicit consent or without the mention of the ethical aspects had a low participation rate and one of the lowest number of participants.

In this context, we concluded that the mention of research ethical aspects increases the participation in epidemiological surveys with data collection through online platforms.

Author´s contributions

PM carried out bibliographic research, quality evaluation, categorization of results, editing and writing of the manuscript. PM and CS performed the crossings of the descriptors explained in the article at the same time until the selection of the final sample, but double-blind. The results of the research were calibrated between PM and CS with 100% accuracy. MS and AM analyzed and interpreted the data, peer-reviewed articles and assisted in quality assessment. All authors read and approved the final version of this manuscript.

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Troponin I as a predictor of mortality in patients with atrial fibrillation in heart failure

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Abstract

Introduction: To determine the predictive value of Troponin I level in mortality for patients in heart failure with atrial fibrillation.

Respondents and methods: Cross-section study analysed the predictive value of Troponin I in 200 patients with heart failure of all ages, both sexes. The study was conducted in the Department of Internal Medicine of Cantonal Hospital "Dr. Irfan Ljubijankić", Bihać, Bosnia and Herzegovina. Considering the leaders of the heart rate, respondents were divided into two equal groups of 100 respondents: the first group were patients in heart failure with atrial fibrillation, and the second group were patients in heart failure with sinus rhythm. All patients with heart failure were clinically examined, with electrocardiogram, ultrasound of the heart, and the value of Troponin I in serum was determined. In the study, the value of Troponin I considered normal if <0,04 ng/ml.

Results: The average age of patients in the first group was 65.0 (8.6) years, and in the second group 65.3 (9.1) (t = 0.215, df = 198, p = 0.83). The first group consisted of 47/100 (47%), while the second group had 41/100 (41%) of female respondents, (X 2 = 0.73, df = 1, p = 0.48). There were more male respondents in both groups. The average value of TNI in the entire sample was 0,31 (0,99) ng/ml (range 0,0-7,2 ng/ml). The average value of TNI in the first group was 0.30 (0.93) ng/ml, and in the second group 0.32 (1.06) ng/ml, (t=0.14; df=198; p=0, 89). In the first group there were 21 (21%) mortality, and 15 (15%) in the second group (X 2 = 0.85, df = 1, p = 0.36). Univariate regression analysis of the first group of respondents TNI shown the relation of chances (odds ratio - OR) of 2,05 (95%CI=1,20-3,48; p=0,008), and when a function of time (hazard ratio - HR) was taken into account, TNI as a predictor was 1,72 (95%CI=1,29-2,29; p<0,001). In the second group of respondents TNI showed OR=1,46 (95%CI=0,97-2,20; p=0,07), and HR value was 1,33 (95%CI=1,03-1,71; p=0,03).

Conclusion: TNI is a significant predictor of mortality in patients with atrial fibrillation in heart failure.

Key words: TNI, heart failure, atrial fibrillation

Introduction

Heart failure is a condition characterised by structural or functional disorders of the heart leading to inability of the heart chambers to receive or displace the blood and thereby transporting oxygen to the body in an amount that body needs. Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia. Atrial fibrillation may worsen existing or to precipitate new heart failure, significantly affects the tolerance of physical activity and quality of life in general, and one-third of all hospitalisations due to cardiac arrhythmias consists of hospital admissions due to atrial fibrillation (Potpara and Polovina, 2011). The risk of ischemic stroke and other thromboembolic complications are significantly increased in patients with heart failure (SI) in the presence of atrial fibrillation (AF). The discovery of biomarkers has led to unprecedented opportunities to study cardiovascular diseases, early diagnosis and better ability for risk stratification, biomarkers targeted therapies and better specification of short-term and long-term prognosis of the disease. Dominant markers that reflect the process of inflammation were discovered, as well as thrombosis / fibrinolysis, neurohormonal activity, intraplaque instability; in other words, better imaging of vulnerable patients and vulnerable blood.

The importance of cardiac biomarkers is given by new studies that are underway and which support the use of the markers themselves in the

diagnosis, prognosis and treatment of heart failure. Troponins are structural proteins of the heart and skeletal muscles. The three troponin complex polypeptides are troponin T (asymmetric globular protein or tropomyosin-binding component), troponin I (basic globular protein that inhibits myosin ATPase depending on the amount of Ca^{++} bound to troponin C), and troponin C (Ca^{++} binding component) which is not heart-specific.

In a study by Januzzi et al (2014), they commented on the role of cardiac troponins cTnI and T in heart failure and stated that troponin is often observed in the context of acute myocardial infarction and should always be suspected of acute myocardial infarction, also that it is common for them to be elevated in patients with heart failure.

Elevated troponin values may further complicate the use of high troponin sensitivity in the assessment of possible acute coronary syndrome, and with this a significant prognostic opportunity is open because patients with elevated troponin in heart failure have a poorer prognosis.

In order to elucidate all these aspects, a multimarker approach is preferred in the diagnosis and stratification of each patient individually (Ćirić-Zdravković et al., 2008).

Establishing a multi-marker strategy to assist prediction of the heart failure risk may increase the ability to identify patients at high risk of mortality and provide information that could be useful in clinical decisions for patients.

AIM

To determine the predictive value of the Troponin I level in mortality in patients with atrial fibrillation in heart failure.

Respondents and methods

A prospective study included 200 patients with heart failure, all ages, both sexes, which were treated clinically and as outpatients at the Department of Internal Medicine at the Cantonal Hospital "Dr. Irfan Ljubijankić" in Bihać.

Respondents were divided into two equal groups of 100 subjects according to heart rate leaders: the first group consisted of patients in heart failure with atrial fibrillation, and the second, i.e. the control group consisted of patients in heart failure with sinus rhythm. All patients with heart failure had clinical examination, electrocardiogram, ultrasound of the heart, and value of Troponin I in serum was determined.

In the study, the value of Troponin I is considered normal if <0,04 ng/ml. Analysis of TNI values was performed with an AXSYM-Abbott analyser using the microparticle-enzyme-immunoassay method.

Statistical analysis was performed in the SPSS 22.0 software package (Armonk, NY: IBM Corp.). The parameters of descriptive statistics were used to show the basic characteristics of the sample. The student's t-test for comparison of quantitative variables was used where possible, otherwise the Mann-Whitney test was used. The chi-square or Fisher test was used to compare categorical variables.

Univariate regression analysis was used to test the predictive potential of variables which were point of interest. The Kaplan-Meier curves were created with determination of log-rank tests for the time to death with comparison of the respondent groups. Cox's regression analysis was made for evaluation of the risk (hazard ratio), with the calculation of 95% reliability interval in order to test the potential of predictive variables of interest, in the function of time. The level of statistical significance of 95% ($p < 0.05$) was considered as the limit of significance for all statistical tests.

Results

The average age of patients in the first group was 65.0 (8.6) years, and in the control group 65.3 (9.1) ($t = 0.215$, $df = 198$, $p = 0.83$). The portion of female respondents in the first group was 47/100 (47%), and 41/100 in the control group (41%), ($X2 = 0.73$, $df = 1$; $p = 0.48$). Median value of ejection fraction (EF) in the first group of subjects was 45% (IQ range: 36-50), while in the control group of respondents was 45% (IQ range: 35-50), ($p=0.49$). The average value (SD) of TNI in the entire sample was 0,31 (0,99) ng/ml, ranging from a minimum of 0.0 to a maximum of 7,2 ng/ml. Taking into account the upper limit of reference values of TNI of 0.04 ng / ml, the entire sample had 35/200 (17.5%) subjects with elevated TNI. The average value of TNI in the first group of subjects

was 0.30 (0.93) ng/ml, and in the control group 0.32 (1.06) ng/ml, (t=0.14; df =198; p=0,89). The frequency of patients with lethal outcome during the follow-up period in the total sample amounted to 36/200 (18%). Comparing the incidence of death, the first group had 21 (21%), and the control 15 (15%) (X2=0,85; df=1; p=0,36). A separate analysis of the predictive potential of TNI in the first group of subjects was performed, univariate regression analysis showed that TNI was a statistically significant predictor of mortality after 12 months in this first group of subjects. Namely, for TNI the odds ratio (OR) of 2.05 (95% CI = 1.20-3.48; p = 0.008) was shown, i.e. for each increase in TNI of 1 ng / ml, the chances of death the outcome grew by 2.05 times. When the time function was taken into account, after Cox's regression analysis, it was found that the hazard ratio (HR) for TNI was 1.72 (95% CI=1.29-2.29; p <0.001), i.e. for each increase in TNI by 1 ng/ml, the risk of death increases by 1.72 times each month. So, also in the survival perspective in the function of time during the 12 months, TNI was a significant predictor of mortality.

Analogous to the above analysis, the predictive potential of TNI in the control group of subjects was analysed separately. TNI was not statistically significant predictor of mortality OR=1,46 (95%CI=0,97-2,20; p=0,07). When the time function (HR=1.33; 95% CI=1.03-1.71; p=0.03) was also taken into account in the control group of subjects, TNI was a significant predictor of mortality over a 12-month period.

Discussion

Despite advances in the treatment of heart failure, mortality remains high, where the five-year mortality rate is almost 50% (Roger VL et al. 2004). Although the risk of mortality in patients with heart failure was previously examined in clinical studies, an individual prognosis could not be assessed. Earlier studies showed that elevated levels of biomarkers, including C-reactive protein (CRP), B-type natriuretic peptide (BNP) and troponin, may be individually associated with an increased risk of mortality in patients with heart failure. TNI is a cardiac specific structural protein that is part of the troponin-tropomyosin complex, but a small amount of TNI exists in the cytosol. Elevated serum TNI level has been documented in a number of cardiovascular diseases, including heart failure. Although elevated serum TNI is an indicator of necrotic myocyte injury during myocardial infarction, the pathophysiology of elevated serum TNI in heart failure is likely to differ from that seen during myocardial infarction. A minor increase in TNI in chronic heart failure, including those identified in previous studies, may mean limited presence, irreversible myocyte injury, and death, or alternatively may represent cytosolic TNI leakage in reversible injury as a result of loss of cell membrane integrity. (Wu AH, Ford L.,1999).

Recent research has focused on the use of cardiac markers in the diagnosis, treatment, and prognosis of patients with heart failure. Taking into account the significant number of patients with heart failure, high mortality and high costs of treatment of these patients, it is necessary to emphasize the importance of risk stratification in heart failure. Markers present in the circulation are used to diagnose and assess risk in patients with heart failure. In addition to being useful as clinical tools, markers can provide us with insight into the foundations of pathophysiology, suggesting new guidelines for fundamental research or the development of new therapies. Measurement of cardiac troponins in heart failure have a fundamental role in the diagnosis and management of acute coronary syndromes. (Thygesen K et al. 2007). In addition to their role in ischemic heart disease, new data support the importance of measuring TNI in acute and chronic heart failure. These observations have broad implications for prognosis, therapy selection, development of new treatments, and understanding of the fundamental mechanisms. (Del Carlo CH, O'Connor CM., 1999).

Conclusion

TNI is a significant predictor of mortality in patients with atrial fibrillation in heart failure.

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
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Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

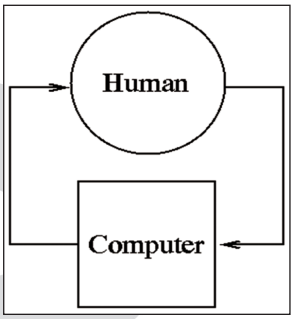

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

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