

A study on side effects of antibiotics used in the treatment of patients with head trauma and legal responsibility of clinicians in terms of the right to health

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Abstract

Aim: Patients with head trauma are routinely, and commonly treated with prophylactic antibiotics, which may also be used for the treatment of infection that may be developed during hospital stay. The relevant antibiotic may, however, have some side effects and adverse events. The present study aimed to investigate whether the side effects and adverse events of the prophylactic antibiotics were considered as a complication or medical negligence.

Material and Methods: Descriptive statistics were used for the evaluation of the data.

Results: No studies were found in the literature. Ceftriaxone, ampicillin-sulbactam, and cefazolin sodium were preferred for antibiotherapy. Meropenem or vancomycin was solely administered to patients when observed active pathogens in culture-antibiogram. Clinicians should be cautioned the potential side effects and adverse events of some drugs frequently used in clinics.

Conclusion: Otherwise, they may legally be held liable for medical negligence.

Keywords: Adverse effect; head trauma; human rights; malpractice; negligence; rational antibiotic use; right to health; side effect; professional liability.

INTRODUCTION

Neurological examination for head trauma should immediately be performed after being summarized the pathophysiology, and accurately identified symptoms. Then, the damage types should be determined considering the level of injury. The medication, of which antibiotics are common, is used for patients with head trauma referred to the emergency departments.

Mannitol solution, furosemide, and phenobarbital that may lead to the development of antibiotic side effects can be administered to the patients with increased intracranial pressure or cerebral edema if no shock or fluid loss is observed after ventilation control is achieved. Patients with a concomitant spinal cord trauma can also be given

preparations containing corticosteroids alongside the mentioned medications (1).

The first-generation cephalosporins are commonly used for the treatment of patients with head trauma. The third-generation ceftriaxone is recommended for the treatment of penetrating brain injury, major contamination or cerebrospinal fluid leak.

Both the first-generation cephalosporins and third-generation ceftriaxone can cause serious allergic reactions. The antibiotics can interact with alcohol and as well as many pharmaceutical preparations. Hypertension, bradycardia, and hypoventilation can be observed in patients with post-traumatic increased intracranial pressure (2). Some antibiotics can also have side effects,

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such as hypertension, bradycardia, and hypoventilation (3).

Symptoms, such as confusion, and unconsciousness can be seen in patients with head trauma, which may lead to the taking of unreliable anamnesis. The data provided by the relatives of patients related to the medical history, drug usage, alcohol consumption may also be misleading.

Potential side effects that result from the use of antibiotics are construed within the scope of the right to health. However, whether the right to health can be considered as a human right is still controversial issue. Progress in human rights and gains in this field has not emerged spontaneously. All are the results of a long-lasting historical struggle. Clashes amongst social classes, and differences in economic status and social structures of society have positively contributed to the emergence of the fundamental rights.

The human rights that evolve gradually in historical process can be classified as generations. The classification based on the concept of generations has been introduced by Carel Vasak in 1979 (4). Vasak sought to justify the idea of human rights classification with famous slogans of the French Revolution of 1789, such as liberty, equality and fraternity (4). The first-generation rights, such as the right to life, right to a fair trial, freedom of expression, are called blue rights that generally involve the political and individual rights. The second-generation rights are called social, economic and cultural rights, including the right to employment, right to housing and healthcare, right to social security, etc. The third-generation rights are called solidarity rights, including the right to a healthy environment, right to natural resources, right to self-determination, etc.

The first-generation rights are the negative rights that require no positive action taken by the public authorities, but the authorities should respect the full enjoyment of the relevant rights and do not infringe on them (5). The second-generation rights are positive rights, and the public authorities should take positive measures to secure the full realization of these rights (6). Unlike the first and second-generation rights, certain social actors should act together to achieve the enjoyment of the third-generation rights. The mentioned social actors include both private institutions and public authorities.

The right to health is recognized as a second-generation right. This right was, firstly, defined as a specific type of human right by the Constitution of the World Health Organization in 1946. The term of "health" has been defined in this document as follows: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (7). The right to health has also been provided as a fundamental right by the following provisions: "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, and economic or social condition" (7).

The right to health was set out as an undetachable part of the right to life in the Universal Declaration of Human Rights in 1948 (8). It also appeared in the International Covenant on Economic, Social and Cultural Rights in 1966. The Committee on Economic, Social and Cultural Rights, the United Nations body that is entrusted with monitoring the fulfilment of the Member States' obligation in terms of the Convention, has defined the States obligation related to the right to health as follows: The Member States should provide access of individuals, including vulnerable and marginalized persons, to the health care services, safe and sufficient staple foods, potable water, sheltering without making any discrimination (9). The committee has underlined that States should fulfil the foregoing obligations according to their financial resources.

The right to health has also been recognized as a fundamental right by the European Council's documents. The duties of public or private institutions to secure effective enjoyment of the relevant right have proclaimed as follows in the Revised European Social Charter (1996): The Member States should eliminate as far as possible the causes of illness, provide advisory and educational facilities for promoting the right to health, and hinder as far as possible endemic, epidemic and other diseases.

Some similar provisions have also been placed in the Oviedo Convention on Human Rights and Biomedicines. The mentioned provisions have prescribed that the member States should provide equal health care services for all the individuals under their jurisdiction. All intervention, including researches, in the field of healthcare service, should be in accordance with the standard rules of medicine (11).

Given the relevant international documents, the states have three main obligations in terms of the right to health, which involve the obligation of respect, protect and fulfil. The States should not obstruct everyone's equal enjoyment of the health care service to implement the obligation of respect, and they should enact appropriate legislation and take other necessary measures to ensure everyone's equal access to the health care services to fulfil the obligation to protect. The privatization should not prevent equal access to the healthcare services and not constitute a concrete threat against the quality and acceptability of the services. The practitioners should be given appropriate education, in-service training, and they have the ability of conducting their profession properly. To achieve the obligation to fulfil, the States should give priority to recognize the right to health as a fundamental right, determine national health policy, make necessary legislation, and establish appropriate healthcare infrastructure, including hospitals, medical schools, and educational institutions.

In Turkish legal practice, the right to health is provided in the article 56 of the Constitution, that is, amongst the economic and social rights. The relevant right is considered as a positive right (12), which means that the State should take positive actions to fulfil its duty on this

matter. The negative aspect of the right has expressed in the judgments of the Turkish Constitutional Court (hereinafter TCC). As stated in the foregoing international conventions, the TCC has concluded that the public authorities also have duties to respect, protect, and fulfil regarding the right to health.

The present study aimed to investigate whether the side effects of the prophylactic antibiotics in patients with head trauma were considered as a complication or medical negligence. Through the findings obtained, legal liability of the clinicians, appropriate usage and side effects of the relevant antibiotics were explained. Subsequently, some suggestions were also made for clinicians

MATERIAL and METHODS

Patients admitted to neurosurgery clinic between 1 April 2016 and 1 April 2019 were included in this retrospective study. Permission was obtained from the hospital director to use the patients' data (Date: /Number).

Pharmacological preparations and prophylactic antibiotics, routinely administered to the patients, were listed. The side effects due to the antibiotic usage were recorded. A comprehensive and systematic literature search of numerous electronic databases, including the National Library of Medicine at the National Institutes of Health, PubMed, was performed. A combination of keywords was used to retrieve studies broadly associated with the topic of interest. The search criteria were as follows: "head trauma," "antibiotic use," "negligence," "side effect," and "adverse reaction."

The headings and abstracts of all studies on the use of prophylactic antibiotics in the treatment of head traumas were reviewed. The full texts of the appropriate studies were retrieved according to the headings and abstracts, and then the decision of whether to include or exclude these studies was made after a comprehensive review.

Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study. Critical appraisal checklists were used to assess and analyze the quality of the selected studies. The obtained data were summarized, and the findings were compiled in a clear and understandable manner using tables. The present study was conducted using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (13, 14). The obtained data were presented as the number, frequency, and minimum-maximum using Microsoft Office Excel (2013)

RESULTS

The mean age of the patients (n=17) was 25.53±20.46 years. Of the patients, three were injured due to a motorcycle accident, three were injured due to a road traffic accident, six were injured due to the fall, and the remaining five were injured following an unintentional fall from height. The patients pre-diagnosed with frontal

fracture (n = 6), temporal fracture (n = 1), occipital hemorrhage (n = 1), epidural hemorrhage (n = 2), subarachnoid hemorrhage (n = 5), parietal fracture (n = 1), were referred to the neurosurgery clinic. The patients with an injury of motorcycle accident had the Glasgow Coma Scale (GCS) between 9 and 12 (min-max), the patients with an injury of road traffic accident had the GCS score of 9 to 15 (min-max), the patients with an injury of fall had the GCS score of 10 to 15 (min-max), and those with an injury of unintentional fall from height had the GCS score of 9 to 15 (min-max).

The patients were administered prophylactic antibiotics, such as ampicillin-sulbactam (n = 2), cefazolin sodium (n = 6) and ceftriaxone (n = 9). The usage duration of ampicillin-sulbactam, cefazolin sodium, and ceftriaxone were 7.00±1.41, 1.17±0.41, and 3.22±1.86 days, respectively.

Klebsiella pneumonia was observed in blood culture of a patient with a temporal fracture, and the relevant patient was subsequently treated with meropenem (3g per day, 14 days). Methicillin-resistant coagulase-negative Staphylococcus was observed in blood culture of a patient with subarachnoid hemorrhage, and as well as a patient with a frontal fracture. The last two patients were treated with vancomycin (2g per day, 10 days). The patient with a frontal fracture was orally given 600 mg rifampicin per day for five days, and 1 g ciprofloxacin per day for a day after discharge from the hospital. No side effects or adverse events were observed in the patients who were administered appropriate antibiotics according to the culture antibiogram results.

One hundred sixty-six thousand eight hundred sixty studies that were published between 1 December 1929 and 30 April 2019 were retrieved using the keyword "head trauma". Of all the studies, 2,621 were related to antibiotics, of which 11 examined side effects, and 15 investigated adverse events of antibiotics. The data extracted from studies were presented through a table. Three studies (15-17) were retrieved using the keyword "negligence". Two case reports (15, 16) were excluded. The remaining study was also excluded since it was related to the psychiatric treatment, and malpractice (17)

DISCUSSION

Head injuries result from exposure of the skull and cerebral tissue to an external mechanical force, which may lead to impairment of physiological stability, cerebral perfusion, and increased intracranial pressure. Two types of primary head injuries are commonly observed. The open head injuries widely involve scalp lacerations and scalp fractures. The closed head injuries involve scalp contusion, concussion, and diffuse axonal injuries. The infection can develop in the scalp lacerations, leading to vein tears. Cerebrospinal fluid leaks, brain abscess, and meningitis can develop due to the damage of dura mater in patients with basilar skull fractures, which can cause infection. Patients with increased intracranial

pressure, epidural hematoma, subdural hematoma, and intracerebral hemorrhage secondary to head trauma can also experience the development of infection.

Patients with head traumas are routinely administered antibiotics. In every case, anamnesis, and patients' history (drug use, alcohol, smoking) should accurately be taken to eliminate potential side effects, and adverse events. Anaphylaxis, defined as life-threatening severe systemic reactions arising from mediators that are released from mast cells, and basophils in the past, is, today, described as a severe systemic hypersensitivity reaction that can be rapid in onset and cause sudden death. (18). Clinicians should also keep in mind that the most serious clinical picture leading to death can occur if the allergy is not accurately diagnosed and treated in time.

Each mechanism, involved in the distribution and expression of the cytochrome P450 (CYP) enzymes, is unique and genetically described. The expressions of CYP can be affected by the endogenous substrates, such as fatty acids, steroids as well as external nutrients, which can also affect drug metabolism.

Most significant factors affecting drug biotransformation are as follows; genetic polymorphism, drug-drug or drug-nutrient interactions, existing diseases, and age. Clinical efficacy, pharmacological effects, and toxicity may change in the treatment depending on the mentioned factors.

CYP3A4 metabolizes most of the prescribed drugs. CYP3A4 inhibitors can lead to the inhibition of warfarin metabolism, which can increase the risk of bleeding. The antibiotics, including ciprofloxacin, clarithromycin, erythromycin, metronidazole, and co-trimoxazole, can also increase the risk of bleeding through the inhibition of intestinal flora. Clinicians should predict the mentioned potential risk of bleeding to avoid complications. The present study aimed to give insight into the points that the clinicians should pay attention while administering antibiotics to patients with head trauma and to examine their legal responsibility in the event of the side effects and adverse events development.

The right to health is counted amongst the fundamental rights in the Turkish Constitution. The international documents regarding the protection of human rights are commonly considered the relevant right as a fundamental right. Recognized as a fundamental right by both national and international law, everyone has the right to health innately, and no one has the right to waive its enjoyment. The right to health imposes obligations on both the public authorities, and third parties in order to protect the health of others, and also necessitates taking necessary steps to prevent any damage to public health. The obligation imposed on the third parties is only to respect the right to health, that is, not give harm to individuals' lives. The public authorities, however, have negative and positive obligations to achieve the full realization of this right. The obligations prescribed by the international conventions are also applicable in the Turkish domestic law.

As recognized by both the national and international law, the right to health is directly associated with the right to life, and the right to protect and improve the corporeal and spiritual existence. To achieve the negative obligations, the public authorities should refrain from the illegal acts that may deteriorate the public health, allow the treatment of patients, and hinder third parties' harmful acts to the health of individuals. The obligation of allowing the appropriate treatment consented by a patient, the right to respect for the privacy of medical records, the right to respect for the free access to the medical reports by patients, the right to be informed before treatment, and the right to refuse medical treatment are also considered amongst the negative obligations (19). In each case, the public authorities should thoroughly monitor and control whether the requirements of the mentioned rights are satisfied by the healthcare personnel working in both private and public hospitals. The State should fulfil its duties related to the negative obligations regardless of the capacity of its financial resources (12).

Alongside the negative obligations, the State has positive obligations, including the obligation to protect and fulfil. The positive obligations related to the right to health that are laid down in the article 56 of the Constitution basically require the regulation of all the health care services provided by the State. Accordingly, the State should plan, regulate, and control the health care services in both public and private health care units.

The positive obligations incumbent on the State should be achieved considering the following criteria; availability, accessibility, acceptability, and quality. The authorities should make available appropriate health care facilities, goods, and services to individuals. An adequate number of healthcare personnel should be employed, and individuals should have equal access to health care services. All economic and physical obstacles that may prevent the equal access to the health care services should be eliminated. The health care services should medically and scientifically be acceptable, appropriate and of high quality. This significantly requires the appropriate training of the health care personnel, the use of scientifically acceptable and approved drugs, and healthcare-related equipment.

The Turkish Constitutional Court (hereinafter TCC) and the European Court of Human Rights (hereinafter ECtHR) had the opportunity to examine the right to health in cases related to the right to life and right to protection of private life. The relevant courts have defined the obligations of the State in terms of the right to health. In addressing a case regarding the right to life, the TCC has concluded that the aim of the protection afforded by the article 17 of the Constitution is to prevent any arbitrary intervention of the State agents that may give harm to corporeal and spiritual existence of individuals. The TCC has also pointed out that the State has substantive positive obligations involving the effective protection of corporeal and spiritual existence of individuals in cases of medical interventions

(20). As laid down in the article 56 of the Constitution, the positive obligations also encompass health care services. In the particular context of health care, the State should make regulations compelling both private and public hospitals to take appropriate measures for the protection of individuals' health (21).

The ECtHR has also taken the same view in cases related to the right to health. The court has emphasized that the member States should make legislation that oblige the public and private hospitals to adopt necessary measures for the protection of the individuals' lives. (22). The ECtHR has stated many times that the right to health is not amongst the rights guaranteed under the European Convention on Human Rights and its Protocols, however, the positive obligations should be implemented for the full realization of the right to health when the right to life is at stake (23).

In cases where medical negligence is alleged in the context of the treatment of a patient, both the TCC and ECtHR has underlined that the State cannot be held responsible for a medical negligence resulting from an error or negligent act of a health care professional when the adequate regulations are made for ensuring appropriate professional standards amongst health care professionals. The TCC and ECtHR have also emphasized that the positive obligations in cases of medical negligence are satisfied if the State provides legal remedies with the patients that allow to establish the responsibility of the person concerned and redress any damages sustained. The legal remedies required can be an action in the civil courts, either alone or along with a remedy in the criminal court.

In Turkish legal practice, the civil, criminal, administrative liability of the health care personnel are set out by the laws. In cases where medical negligence is asserted, the victims are entitled to bring a civil or administrative action against the personnel concerned. They also have the right to file a criminal complaint with the prosecutor's office. Whichever legal remedies are made use of by the victims, the liability of the health care personnel is at stake if the person concerned do not comply with the standard, approved rules of their profession. Hence, the health care professionals should adduce evidence demonstrating the conduct that has complied with the standard rules of the profession. The practitioners are also expected to act professionally according to the standard of care that would be expected of a similar careful, reasonable practitioner under similar circumstances.

The use of preoperative prophylactic antibiotics is one of the main modalities to prevent surgical site infections. Beta-lactam antibiotics are commonly preferred class of drugs, of which cefazolin is the most widely used, for the treatment of infection. Patients with a weight < 80 kg should be given 1 g antibiotic, patients with a weight between 80 and 120 kg should be given 2 g antibiotic, and patients with a weight >120 should be given 3 g antibiotic 30-60 min before surgery. The reuse of the same dose

antibiotic is recommended if patients lose blood over 1,5 L during surgery, or if the surgery continues over 4 h. Although ceftriaxone is not often preferred for surgical prophylaxis, it can be used in some particular cases. Beta-lactam antibiotics can cause hypersensitivity reactions. Penicillin allergy should preoperatively be assessed. Patients with a history of allergic reactions should be accepted as positive, and other agents should be used for prophylaxis.

Suspected perioperative hypersensitivity reactions are rare, but significantly lead to the morbidity and mortality following surgical interventions. Recent studies have suggested that the potential allergenic effects of drugs may differ amongst the countries, and that novel allergen may emerge through changes in the molecular pattern of causal agents (24).

In the present study, the heterogeneity was planned to be evaluated using a random effects model or a fixed effects model. In picking this method, the first aim was to make different assumptions about all the obtained results. The second aim was to establish a fixed value for the results extracted from the whole population, such as fixed-effect meta-analyses. The study aimed to collect the data of all the studies that have previously investigated adverse events and side effects of prophylactic antibiotics used for the treatment of patients with head trauma, and to make an overall assessment of the data extracted. However, the meta-analysis of the data, including a mathematical combination, could not be performed since no common data were found and the results were, thus, presented as a systematic review. Such a presentation was not a limitation of the study. The retrospective design used for the evaluation of the data was, however, a limitation of the study. In addition, descriptive statistics were only presented due to the small number of patients.

CONCLUSION

Neurosurgeons may not prevent the introduction of a novel drug with a lethal interaction potential into the market, and not know all the possible drug-drug interactions. However, they should be aware of the potential side effects and adverse events of some drugs widely used in clinics. If necessary, medical pharmacology experts should be consulted before planning of the treatment. Otherwise, they may legally be held liable for the side effects and adverse events of the relevant drugs.

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