Author’s response to reviews

Title: Legal medicine implications in fibrinolytic therapy of acute ischemic stroke

Authors:

Monica Sabau (sabau.monica@yahoo.com)
Simona Bungau (simonabungau@gmail.com)
Camelia Liana Buhas (cameliabuhas@yahoo.com)
Gheorghe Carp (spitalul.judetean@rdsor.ro)
Lucia Georgeta Daina (lucidaina@gmail.com)
Claudia Teodora Judea-Pusta (claupustaml@yahoo.com)
Bogdan Adrian Buhas (buhasbogdan@yahoo.co.uk)
Claudia Maria Jurca (claudiajurca70@yahoo.com)
Cristian Marius Daina (cristi.daina@yahoo.co.uk)
Delia Tit (mirela_tit@yahoo.com)

Version: 2 Date: 23 Jun 2019

Author’s response to reviews:

Date: 23/06/2019

Subject: Your Submission METH-D-19-00031R1

Ms. Ref. No.: METH-D-19-00031R1

Title: Legal medicine implications in fibrinolytic therapy of cerebral vascular accidents

Journal: BMC Medical Ethics

Dear Ana Donnelly

On behalf of

Liam Messin
We are very thankful to the Editor/Reviewers for their notes; we have carefully read the comments and have revised / completed the manuscript accordingly. Our responses are given in a point-by-point manner below, as well all the changes and completions to the manuscript are highlighted in red and our comments for the editor in blue.

The authors mentioned (in the initial list of authors) in 2nd and 8th positions (Gabriel Constantin Mihalache and Cristian Sava) requested to be removed from the authors list because their initial contribution to this paper was minimal and they are not available for the Major revision requested by the Editor. In the Acknowledgements. The following text was added: As well, they express their appreciation to Gabriel Mihalache MD and to Cristian Sava MD for providing initial information regarding this paper. At the same time, considering that we need experts in ethics, bioethics and legislation (as recommended by Reviewer 1), we asked two colleagues experienced in the field (Simona Bungau and Delia Mirela Tit) to deal with revision and, implicitly, with the issues of the legislation mentioned; so, they both were added as coauthors. All the other authors agreed to this replacement.

Reviewers/Editor reports:

N. V. Todd (Reviewer 1): I liked this paper in principle but it has a number of problems. I emphasise that I will comment upon the law as I see it from a UK perspective. I have no knowledge of Romanian law, if that is different. The subject of the paper is relevant and interesting. However the analysis of the legal principles it is flawed.

In many places they say that informed consent is mandatory; this is incorrect. It is correct for elective procedures, but not in an emergency. In traumatic head injury (as one of many examples of emergency treatment) the patient will commonly be unconscious and unable to give consent. Neurosurgeons can treat on the legal basis of the best interests of the patient. If there is a complication of surgery the doctor's defence is necessity (to understand this imagine pulling a man out of the pathway of an oncoming car during which you dislocate his shoulder; it was necessary to pull him away to save his life, the complication is unfortunate but not negligent). Many of the principles of best interest judgments in neurosurgery (and many other disciplines) apply to thrombolysis for stroke.
I will deal with the cases putting in my analysis of the law:

Case 1. The patient had a stroke but the timing of stroke was not known. This, in all of the guidelines, prohibits fibrinolysis. The family complained. Doctors cannot be pushed to treat patients beyond the limits of the scientific knowledge. The decision not to treat was medically and legally correct.

Case 2. Very similar to case 1. The CT demonstrated a stroke that contraindicated treatment. Doctors cannot treat outside accepted guidelines (if they exist).

Cases 3 and 4. The patient could not give informed consent, the family refused consent. The doctor's duty of care is to the patient not the family. Applying the best-interest test treatment should have been given. It is obviously desirable to keep the family informed and to be sympathetic to their views but they cannot prevent necessary treatment. In neurosurgery we faced this decades ago when it was thought that we needed to obtain the relatives consent to switching off a ventilator in a brain dead patient. We do not need their consent, ventilation has no benefit to such a patient and can be discontinued.

Case 5. Perfect management. Thank you.

Cases 6 and 7. Patients who are legally competent have the right to refuse any and all treatments even if their decision is illogical and/or a threat to their life. the patient can, of course, change their mind.

I liked the paragraph at lines 322-329. Thank you.

The idea of a paper that addresses informed consent in treating stroke patients within the very tight timeline for fibrinolysis is interesting and potentially useful. I note that none of the authors is a legal or bioethical expert and, I am afraid this shows. I recommend that the authors take on someone who has such expertise to reframe the legal issues appropriately. This would lead to some interesting conclusions. Cases 1, 2, 5, 6 and 7 were managed correctly. Cases 3 and 4 were not.

We added two coauthors who are teaching ethics/bioethics; they also have experience in this medical field. We hope their corrections/completions will be found satisfactory by the Reviewer.

The Discussion section was corrected and completed with the following text:

The therapeutic protocol for thrombolytic and endovascular treatment in acute ischemic stroke in Romania (valid at the time of this study) was approved by a Ministerial Order. This protocol stipulates the obligation to obtain informed consent for thrombolysis. There is only one exception, namely when the patient does not have the capacity to express his or her consent and/or there are no caregivers: "The patient will be informed about fibrinolytic therapy and will
sign a consent form. The consent form includes information on both fibrinolysis and on the possibility of intra-arterial thrombolysis or thrombectomy, initially or after i.v. thrombolysis. If he can not sign, the verbal agreement will be recorded in the presence of a witness. If the patient can not express his agreement, the family can sign the consent form. If there are no caregivers, and the patient is confused, aphasic or has altered state of consciousness, the doctor can make the decision for thrombolysis if all the inclusion and exclusion criteria are met, the fibrinolytic treatment being included in the Diagnostic and Treatment Guide for Ischemic Stroke with indication Class IA.

On the other hand, Law no. 46 of January 21, 2003 (patient's rights law), with subsequent modifications and completions, stipulates in Article 15: "If the patient requires emergency medical intervention, the consent of the legal representative is no longer necessary", and in Article 17: "...if the legal representative refuses treatment or a medical procedure and the physician considers it to be in the patient's interest, the decision is rejected by an arbitration comission consisting of 3 doctors, for hospitalized patients, and 2 physicians for ambulatory patients"[27]. Both regulations are compulsory, their non-compliance producing legal effects in the case of complaints formulated by the patient. Performing thrombolysis in acute ischemic stroke is a medical emergency, taking into account the narrow therapeutic window, but the specific protocol for this intervention provides only one exception from obtaining the informed consent - the one described above. Thus the dilemma in therapeutic decision making appears. In the particular cases presented (3 and 4), the doctors decided to follow the rtPA specific protocol. The situations of Emergency Exception to Informed Consent in the case of rt-PA administration in acute ischemic stroke described in the literature [28] do not fully coincide with the Romanian protocol, and implicit consent management is permitted if there are no easily accessible sources of consent. If it is established that direct consent can not be provided by the patient, and also to avoid death or severe impairment of the patient, when no other form of consent can be obtained in time, implied consent remains more relevant for candidates for IV treatment with rtPA [29]. An exception to informed consent may be invoked by a physician, if he has proper legal grounds, but the physician's decision to apply the treatment without the informed consent raises an important ethical issue, namely whether the quality of being a doctor is sufficient to make a moral decision on behalf of another person [30]. Whenever possible, it is imperative that the physician obtains a direct consent from the patient candidate for i.v. rtPA therapy, taking into account the moral difficulties inevitable in alternative forms of consensus [28].

There needs to be correction of the text from an active English language speaker.

English was revised.

I hope the authors are happy to revise this because I think it would be a good paper.

Thank you for your suggestion. We made all the necessary completions and corrections.
Paolo Fais (Reviewer 2): Please indicate clearly, maybe at the end of the background paragraph, the aim of this study.

At the final of Introduction section, the aim of the study was added.

Our research presents the problems that arise in front of the neurologist in the process of obtaining the patient's consent with over-acute vascular accident and the negative way in which these circumstances are reflected over the interval of intervention / treatment. On the other hand, there are cases where families expressly require this type of treatment, but patients are out of the criteria: clinical or time.

ABSTRACT

"Conclusion: Obtaining informed consent is a mandatory procedure, which takes time, to the detriment of application of fibrinolytic treatment and therefore, we propose and therefore, we propose to simplify or even drop the consent, considering that acute stroke represents a major medical emergency. After saying "Obtaining informed consent is a mandatory procedure" you suggest to "drop the consent". Instead of making proposals, which of course could not be based on a small case series, maybe would be better to report an apparent unfavourable risk-benefit ratio between a complete shared decision making process and a proper therapy. It may indicate a expedited shared decision making process in selected cases to achieve a timely fibrinolytic treatment. I suggest a rephrasing being more cautious, maybe more studies are necessary to recommend "to drop" the consent for this kind of therapy which of course may lead to serious haemorrhagic complications even when properly and timely administered.

Thank you for the suggestions. Following your suggestions, the part you referred to was removed and new discussions have been formulated about getting informed consent (please see the text in red, in Discussion section).

In Abstract we reshaped the phrase: Obtaining informed consent is a mandatory procedure, which takes time, to the detriment of application of fibrinolytic treatment.

BACKGROUND

Line 37 typewriting error "10 ut" is "10 out"

Corrected.
We removed it.

Assuming that you say "The protocol used for the application of the treatment is extremely clear, in concordance with the European and local guidelines, furthermore being updated few times" do you think it is necessary to explain in detail the Romanian protocol to treat CVA? Maybe would be more interesting to specify and discuss the differences between the Romanian protocol and the European guidelines. What are the differences? Why do they differ? Are differences based on social reasons, economic reasons or what?

We reshaped the paragraph:

The protocol used for the application of the treatment is extremely clear, in concordance with the European and local guidelines, furthermore, being updated several times. There are no and there were no differences between the Romanian protocol and the European guidelines. The latest therapeutic protocol for thrombolytic and endovascular treatment in acute ischemic stroke implemented nationwide was developed in 2018 according to some documents [15-17].

I can't understand what do you mean…

In Romania legal medicine issues were yet present before the advent of fibrinolytic therapy (not treaty, tpw error!)?

Please explain better what do you mean

Sorry for mistake. We rephrased as follows:

Fibrinolytic therapy has emerged as a "standard gold method" for the treatment of stroke, although this type of treatment is at the beginning in Romania; prior to the occurrence of this therapy, aspects of legal medicine involved in this field of medical expertise have already been reported, the doctors being afraid of bleeding complications. Experience has shown in most cases that physicians do not seem to be prepared to cope with emergency situations when they have to obtain the consent of the patient or his care giver, being constrained by time, the informational level of the population, observance of the legal issues, etc.
"At Oradea Emergency County Hospital since March 2012 when this type of treatment was started, fibrinolysis was used in 200 cases of acute CVA. This accounts for approximately 3% of the total acute CVA cases”.

Is it the 3% of the total acute CVA cases in line with the western countries? If no explain or almost hypothesize why.

The percentage reported in our case - 3%, is lower than those reported by similar studies (about 6% in India or less than 7% in the US) [18,19].

In Romania, the introduction of thrombolysis is an important service development for acute stroke services, which was implemented a few years later than in Western countries. At the time of reporting these cases, there were only 7 hospitals in the country where thrombolysis was performed. The lack of centers in each county and the poor road infrastructure in the country determine the increase of the time necessary to get to the hospital. Therefore, the most common cause that impedes venous thrombolysis is exceeding the 4.5 hour therapeutic window. The causes are multiple and are associated with the pre-hospital stage; among the most frequent are: the patient's ignorance of stroke symptoms and implicitly the unawareness of the onset of the disease, as well as the inefficient management of the patient with stroke by the intervention teams.

In 2018, only 14 hospitals in Romania performed this service. Basically, over 75% of the counties did not benefit from a single adequately equipped hospital, where the thrombolysis procedure would be applied for the cases of ischemic strokes, while the other counties benefited from a single hospital. This critical situation has determined the Ministry of Health to take measures to extend the program nationwide. As a result, since the beginning of 2019, more than 95% of the counties have at least one hospital where thrombolysis is performed. By Order of the Minister 170/2019 the protocol for interventional treatment of patients with acute stroke was approved - a set of measures, procedures and directions regarding the care of the patient with acute stroke in the pre-hospital stage, in order to increase the efficiency of the emergency system, as well and in the hyperacute phase (within hospitals).

These measures, along with public education programs to quickly recognize the signs of stroke, and the training of intervention teams for effective management of the patient with stroke in the therapeutical time window for thrombolysis, aim to increase the number of patients receiving this treatment.


Please use "imaging" instead of "imagistic" along the text.

Corrected

Line 353-6:
"It is more common to have a complaint filed in situations of omission because, legally, an action that was unsuccessful but which was done for the benefit of the patient is less contentious than the lack of action which passively consumes the patient's possible chances for recovery".

Please specify that this statement could be suitable for this specific setting (i.e. therapy of cerebrovascular accidents) but not for many other medical settings.

The paragraph you referred to was completed.

In case of emergency interventions in acute stroke, it is more common to have a complaint filed in situations of omission because, legally, an action that was unsuccessful, but which was done for the benefit of the patient is less contentious than the lack of action which passively consumes the patient's possible chances for recovery.

Line 273-4
"the discussion will be focused on the interpretations of these documents through the angle of forensic training and practical application"

I can't understand which documents will be considered and interpreted in the discussion…

We apologize for mistake; we have replaced "documents" with "cases".

Line 276-8
I think physicians encounter occasional issues in applying fibrinolytic therapy. This sentence seems misleading, please rephrase.

Sorry for mistake. We rephrased it.

The presented cases show the difficulties that physicians encounter when applying fibrinolytic therapy. The decisions made by physicians are questioned by the patients or by their relatives.

Your casuistry lead to hypothesize Romanian doctors lack of shared decision making skills. It seems there is and insufficient or a inadequate communication between patients/their relatives
and medical doctors. Please discuss this possible explanation and propose a possible solution (for example, proposal of training programmes aimed at implementing the skills in shared decision making, implementation at a national level of information of the general population about therapy of CVA, ecc).

We added in Discussion section

In the therapeutic decision-making process, obtaining informed consent enables patients to express their opinion on the benefit-risk ratio for thrombolytic therapy, the effect of thrombolysis and various stroke outcomes. Given that antithrombotic therapy should be given in the utmost urgency, the discussion between the patient or his/her family and the clinician in order to obtain informed consent for thrombolysis may be problematic [36].

Time limits as well as the impact of stroke were the factors that helped design an adequate form in terms of knowledge transmission and content to help making the right decisions in urgent circumstances. The need to make a quick decision on the treatment with rtPA means there is not enough time for reflection. The information assimilation is difficult for the patient and family due to the shock of the event and the patients' cognitive deficits and may generate problems during the decision-making period. In this regard, patients often wanted to let the family decide, but their abilities were also compromised. Emotional and social support has been requested by patients both from family members and from people within their social trust area. The expertise of physicians and health specialists was the basis for making decisions about the treatment with rtPA. The patients and their family described the communication as patronal or paternalist, expecting their views to be respected [37].

In the decision to use i.v. thrombolysis as with any treatment, consent can not be assumed, but the physician's contribution to decision-making is essential [38]. In the cases presented in the study, that ended with the refusal of the patient, respectively of the legal representative, their decision was a firm one, which did not allow the intervention of the doctor, in order to change it.

"Prognostic elements are uncertain, especially in the first hours which the main problem revolves around determining the hours until death. For the remaining, neither literature nor statistics gives convincing prognostic elements, especially for the worried relatives, who see an element of hope in the fact that a chance exists for recovery/survival. It is also true that it is difficult to set a clear boundary between an unfavourable evolution, a non corresponding standard of care and a medical mistake. Frequently patients or their relatives project their anger and frustration upon the physician who couldn't assure the healing process. In these situations decision making becomes difficult.
Furthermore, complaints can also have as their mere goal the obtainement of a material benefit, and in this setting, they use every possible method of interpretation from the medical documents or specialist testimony."

This long dissertation it is too generic and seems useless considering the logical frame of this paper.

Thank you for the observation. The text you referred to was removed.

Please rephrase and revise the English of the following sentence "357 Mistaking in action gives the doctor the possibility to correct himself / herself; but mistaking 358 through passivity, he does not have the same possibility: both his chance (to feel the 359 fulfillment of the duty as satisfied) and the patient are lost."

Sorry for mistake. We deleted it.

A more detailed discussion on the reasons leading to the lack of consent to fibrinolytic therapy seems mandatory. Is there any literature on similar issues? Which are the reasons of the refusal to perform the fibrinolytic therapy? What are the possible solutions proposed from the available literature? What are the possible solutions do you propose?

At the final of Discussion section, the following text was added:

In the cases presented in this study, the patient, ie the patients who refused fibrinolytic treatment, invoked the fear of hemorrhagic risk. In our center, we found a decline rate of approximately 2% over the study period, a smaller percentage compared to those reported by other studies [39]. We have also found that there has been a downward trend in refusal over the last few years. The experience accumulated by physicians over time both in conducting the thrombolysis procedure and in relation to patients or their legal representatives, the results obtained and the recent scientific evidence that reported t-PA safety for patients with mild symptoms too [40], may influence positively the doctors' behavior and, implicitly, the increase of patients' confidence in the benefits of therapy [39]. Also, the recent efforts of the Ministry of Health to raise awareness among the public about the alarming signs of ischemic stroke, showing the benefits of thrombolysis, and the need for treatment may be associated with this decrease.

Some data associate the patient's refusal with mild symptoms and with the fact that the patient does not realize the severity of the condition, refusing to accept the hemorrhagic risk [36].

There is little data in the literature related to this topic. Standard care refusal was previously looked into from the ethics perspective [41,42]. From the authors' point of view the physicians have the moral responsibility to deal with patients' refusal and try to correct the patients'
decisions. Though the patient constantly refuses a treatment, proper and competent efforts should be made to enforce the intervention if the refusal affects the individual or the society. Despite the different opinions about the model of medical care, investigators admit that the role of the physician is not to formulate competence or to take decisions that impair individuals or society using the principle of liberty. The refusal should be studied in all cultural, psychological, behavioral, social and ethical context.

Please revise the English.

Revision has been done.