ELICITATION WITHIN EHTA: POTENTIAL EFFICACY OF MELATONIN MEDICATION FOR STEMI PATIENTS WITH DETECTED HIGH RISK OF REPERFUSION VENTRICULAR FIBRILLATION DURING PCI

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Abstract

Patients with acute ST-segment elevation myocardial infarction (STEMI) have a high risk of ventricular fibrillation. The aim of the study is to determine an unknown parameter of the new diagnostic cardiology technology model created within eHTA, effectiveness of intravenous administration of high doses of melatonin (4 mg/kg) before/during PCI as protective medication in STEMI patients with a diagnosed by new technology high risk of ventricular fibrillation at reperfusion using expert elicitation. Ten experts took part in the elicitation and filled out prepared questionnaire, which included experimental evidence for antiarrhythmic action of melatonin, including cellular mechanisms. They expressed their opinions on the potential effectiveness of medication using numerical method and also answered questions about the suitability of the dosage, adverse effects and the risk-benefit ratio. Experts' answers to the main research question were weighted based on their experience. Elicitation revealed the effectiveness value of 71.82% for the tested medication. Eighty percent of experts agreed that the dose is adequate, that side effects will be minimal, and that the benefits of such therapy outweigh possible risks. Results of this study will be applied for eHTA of novel diagnostic technology in cardiology and will help its manufacturer to evaluate the clinical effectiveness of the technology, find the right direction to complete the design and development of medical device, achieve optimal efficiency, present the concept and find investors, prepare for clinical evaluation, CE certification and inclusion to reimbursement system.

Keywords

elicitation, eHTA, melatonin, reperfusion ventricular fibrillation, STEMI, PCI

Introduction

Early stage health technology assessment (eHTA) is evaluating method to determine perspective of a new technology and necessity of changes or design and development modification of technology. eHTA is usually used for determining the economic indicators of new health technologies and deciding on their future development [1].

The technology under eHTA evaluation is a software (SW) module for predicting the risk of reperfusion-induced ventricular fibrillation (rVF) during percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI). The principle of SW is the analysis of the ECG according to a special algorithm, and the result is a report on the presence of a high risk of rVF during PCI with sensitivity of 58% and specificity of 73% [2].

For diagnostic technologies, an inseparable part of a comprehensive view and such analysis as eHTA is the reaction to the results of diagnostics [3, 4]. The entire diagnostic-treatment procedure should be evaluated. Because diagnosis by itself does not cure or improve the quality of life of patients [5]. A prerequisite for future medication as reaction for detected high risk of rVF

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during PCI in STEMI patients is the intravenous (i.v.) administration of melatonin in high doses (4 mg/kg) before/during PCI.

The unknown parameter of the model created within eHTA is only effectiveness of the new medication in the group of STEMI patients with detected high risk of rVF during PCI. According to a systematic literature review, no comprehensive analysis, information and statistical data on clinical trials regarding the use of melatonin as an rVF protector for STEMI patients has been reported or published. The effect of melatonin on the occurrence of rVF was mostly studied in animal studies [6–9]. Therefore, within the framework of eHTA, elicitation methods have been used to find out the expected effectiveness of rVF-protective therapy in patients. This study was aimed to determine effectiveness of i.v. administration of high doses of melatonin (4 mg/kg) before/during PCI using expert elicitation.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine hormone synthesized mainly by the pineal gland and directly released into the bloodstream. It is an ancient molecule which presence is not limited to vertebrates. It also occurs in invertebrates, unicellular organisms and plants, although none of them have a pineal gland [10]. However, there is also "extraspinal melatonin production". Melatonin has been identified in a variety of tissues and organs such as the brain, retina, lens, and gastrointestinal and reproductive tracts. In non-primate mammals (although with exceptions) it is also produced in the Harderian gland [11].

It is thought that melatonin first appeared when organisms began using oxygen, and its original role was to neutralize toxic O_2 derivatives (free radicals and reactive oxygen species), thus acting as an antioxidant [12]. Although the structure of melatonin has remained unchanged, its original role as an antioxidant has been supplemented by numerous other effects throughout evolution [12, 13].

Once released into the bloodstream, melatonin has several effects, some of which are receptor mediated. In humans, two types of receptors (MT1 and MT2) have been characterized. Located in most peripheral tissues and the central nervous system, MT1 and MT2 are transmembrane receptors that belong to a family of G protein-coupled receptors, which act through second messengers, including adenylyl cyclase, phospholipase A2, and phospholipase C, thereby modifying the production of cAMP and cGMP or diacylglycerol and IP3 [13, 14].

In addition, a third cytoplasmic melatonin receptor, called MT3, was later identified as a quinone reductase enzyme, whose function is to inhibit the electron transfer of quinones and thereby protect against oxidative stress [13, 15].

The only receptors in humans that have been found to play a role in the cardiovascular system are MT1 and MT2, as they are present in the cerebral arteries, coronary arteries, systemic arteries, aorta, and ventricular cardiomyocytes [16, 17]. These findings support the idea that melatonin may have a significant impact on cardiovascular diseases and their complications [13, 18].

Melatonin has been proposed for use in ischemic/reperfusion conditions as a cardioprotective drug [19–22] and its antiarrhythmic properties have been demonstrated mostly in experimental models [6–8, 23–26]. Melatonin has been shown to induce a variety of electrophysiological effects in the myocardium. Specifically, it dampens the shortening of action potential duration in the ischemic area [7] and increases the expression of connexin 43, thereby contributing to the improvement of conduction velocity in the ischemic myocardium [27]. Both effects may be related to the antiarrhythmic action of melatonin [9, 28].

Animal studies

The influence of melatonin on the occurrence of reperfusion ventricular fibrillation has been addressed by several animal studies. In the work of Sedova et al. [9], the association between the occurrence of ventricular tachycardia and/or ventricular fibrillation (VT/VF), oxidative stress and myocardial electrophysiological parameters in experimental ischemia/reperfusion under melatonin treatment was evaluated. Melatonin was administered to 28 rats (10 mg/kg/day, orally, for 7 days) and 13 animals were administered a placebo. In anesthetized animals, the occlusion of the left anterior descending coronary artery was induced for 5 min followed by reperfusion with recording of unipolar electrograms from the ventricular epicardium using a 64-lead matrix. The melatonin group showed a lower incidence of VT/VF compared to the control group (29%, versus 69%, $p = 0.020$) [9]. Melatonin treatment was also associated with shorter baseline activation times (AT). In vitro, melatonin led to a more complete recovery of action potential duration and resting membrane potentials upon reoxygenation. Thus, the antioxidant properties of melatonin were associated with its effect on the duration of repolarization, while the antiarrhythmic effect was associated, according to the authors, with its effect on ventricular activation independent of oxidative stress [9].

In a study by Tan et al. [6] the authors hypothesized that cardiac arrhythmias during ischemia/reperfusion are related to free radicals generated in the heart, especially during the reperfusion period. Because melatonin functions as a free radical scavenger and antioxidant, the molecule's ability to influence cardiac arrhythmias has been investigated. Melatonin reduced the incidence and severity of ischemia/reperfusion-induced arrhythmias caused by anterior descending coronary artery ligation in the isolated rat heart [6]. Melatonin was administered either infused during the

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period of ischemia and reperfusion or only during reperfusion. The percentage of cases that developed rVF was recorded at the Table 1 [6].

Table 1: The percentage of cases that developed ventricular fibrillation during reperfusion [6].

Group	Period of infusion	Number of probands (n)	rVF incidence rate (%)
Controlling	-	10	90
Melatonin 1 µM	I, R	10	50
Melatonin 10 µM	I, R	10	20
Melatonin 50 µM	I, R	10	30
Melatonin 10 µM	R	10	40

I – ischemia; R – reperfusion.

The authors concluded that in addition to melatonin's function as a broad-spectrum free radical scavenger, melatonin may also reduce cardiac arrhythmias through its regulation of intracellular calcium levels, i.e. by preventing calcium overload, or through its ability to suppress sympathetic nerve function and reduce adrenergic receptor function in myocardium [6]. It was also noticed by authors that the low toxicity of melatonin may bring closer the perspective of its use in patients with ischemic heart disease and arrhythmias. They also consider it appropriate to test melatonin in clinical trials for the prevention of possible ischemia/reperfusion-induced arrhythmias during bypass surgery, vascular spasms of the coronary arteries, or patients with thrombolytic therapy [6].

A study by Diez et al. [7] reported that reperfusion after a short period of myocardial ischemia triggers ventricular arrhythmias attributable to ion imbalance and oxidative stress. Melatonin provides some degree of protection, but its effects on cardiomyocyte electrical potential are essential in realization of antiarrhythmic action. The effects of 5, 10, 20, and 50 µM melatonin were evaluated in isolated perfused rat hearts subjected to 10 min of regional ischemia. Melatonin reduced the incidence of reperfusion arrhythmias from 100% in the control group (n = 11) to 50% in the 5 µM (n = 10) and 10 µM (n = 10) groups, to 40% in the 20 µM (n = 10) and 30% at 50 µM (n = 10). The authors concluded that melatonin reduced the incidence of reperfusion arrhythmias due to its antioxidant effects. In addition, when 20 and 50 µM melatonin was administered, a prolongation of the action potential duration was noted, which, according to the authors, supports improved protection, and this effect should be taken into account when melatonin application in vivo is considered [7].

A study by Diez et al. [8] was based on the fact that although melatonin has been proven to reduce the incidence of reperfusion arrhythmias when administered before coronary occlusion, but in the clinical context of acute coronary syndrome, most therapies are administered only at the time of reperfusion. However, patients often have different pathophysiological background that can reduce the response to therapeutic interventions. The work was focused on investigating whether the administration of melatonin starting from the moment of reperfusion protects against ventricular arrhythmias in Langendorff isolated hearts from fructose-fed rats (FFR), a dietary model of the metabolic syndrome, and from spontaneously hypertensive rats (SHR), all three-month-old Wistar Kyoto (WKY) strain rats. In both experimental models, authors confirmed metabolic changes, a decrease in the total antioxidant capacity of the myocardium and an increase in arterial pressure and NADPH oxidase activity. A decrease in endothelial nitric oxide synthase (eNOS) activity was also detected in the FFR group. Melatonin administration (50 µM) initiated at reperfusion after 15 minutes of regional ischemia reduced the incidence of ventricular fibrillation from 83% to 33% in the Wistar strain Kyoto (WKY), from 92% to 25% in FFR and from 100% to 33% in SHR ($p = 0.0361$, $p = 0.0028$, $p = 0.0013$ respectively, each group $n = 12$). Although the incidence of ventricular tachycardia was high at the onset of reperfusion, the severity of arrhythmias gradually decreased in melatonin-treated hearts. Melatonin induced a shortening of the duration of action potential at the beginning of reperfusion and a faster recovery of the amplitude of the action potential in the SHR group. The authors thus concluded that melatonin protects against ventricular fibrillation when administered during reperfusion, and these effects are preserved in rat hearts exposed to major cardiovascular risk factors. These results, according to the authors, support the continued transfer of this substance into clinical trials [8].

The novel mechanism of antiarrhythmic action of melatonin was established recently, where connexin and sodium channel protein expression, functional state of the connexins and transmembrane sodium current were assessed on isolated cardiomyocytes [29]. The increased conduction velocity in myocardium having an antiarrhythmic effect was due to an enhancement of sodium channel protein and amplification of sodium current. The expression of Scn5a gene encoding the Nav1.5 channel was significantly increased in rat myocytes treated with melatonin. The expression of connexin remained unchanged after melatonin application, despite the increased expression of Gja1 gene transcripts encoding gap junction protein alpha 1 in melatonin-treated animals [29].

In the aforementioned studies, melatonin demonstrated antiarrhythmic properties under ischemic/reperfusion conditions and consistently prevented the development of rVF in rodents in vivo or on isolated heart preparations.

Estimated dosage for patients

Information and statistical data on clinical trials or patient studies regarding the use of melatonin for STEMI patients undergoing PCI with diagnosed high risk of rVF have not yet been published, which is

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common for new developing technologies in healthcare. That is why the eHTA concept takes into account such a situation and there is the possibility of using the elicitation of experts.

However, firstly it was necessary to supplement the description of the expected therapeutic procedures with the dosage of melatonin for human patients.

Research by Sedova et al. [30], which investigated whether terminal T-wave inversion (TTWI) on initial ECG (before reperfusion) can serve as a predictor of rVF in patients with anterior STEMI undergoing primary PCI, among others, confirmed the previous experimental/simulation findings and showed that the mechanisms of origin and methods of rVF prediction are compatible for experimental and clinical setting [30]. Therefore, an analogous rVF-protective effect of melatonin in patients can also be assumed.

To determine the expected amount of medicine administered to human patients, a form of brainstorming was chosen with the participation of one of the research groups, which deals with the effect of melatonin on reducing the risk of rVF. In conclusion, it was assumed that patients with STEMI indicated for PCI would be administered melatonin in the amount of 4 mg/kg before reperfusion. In addition to physiological parameters and information on the effects of melatonin on patients, a pig study using an identical dose (4 mg/kg, intravenously) was considered [31]. This study aimed to evaluate the effects of melatonin treatment on electrocardiogram (ECG) parameters reflecting the main arrhythmogenic factors and to test the association of these parameters with the occurrence of ventricular fibrillation during ischemia episode [31].

Adverse effects

Adverse effects that may occur after administration of melatonin are more often directly related to the pharmacological profile of this drug or its metabolites. There is a great analogy between melatonin and serotonin (its precursor) in terms of their pharmacological targets [32].

Administration of daily doses of up to 300 mg of melatonin without clinically significant adverse effects has been described in the literature [33, 34].

Methods

Expert elicitation is used as a classic procedure within eHTA. Questionnaire was prepared for the elicitation of experts, the main objective of which was to determine the value of the assumed protective effectiveness of melatonin in STEMI patients with a predicted high risk of rVF indicated for PCI. The protective efficacy parameter of melatonin is defined as the elimination rate of rVF in patients who would have developed this complication if no pre-treatment had been administered.

Based on previous research [35], the numerical method was chosen as the main elicitation method. However, it was decided to withdraw from interval methods, as the result of aggregation and processing of answers obtained by interval methods is complex for normal processing by manufacturers of medical devices, does not have a clear methodology and brings significant scattered results that may not be sufficiently usable and informative.

Grigore et al. [36] assumes that in most cases 6 to 12 experts should be sufficient for eHTA research elicitations. Our research [35], which was carried out with the participation of 8 experts, also appeared to be sufficient.

Fifty-eight experts employed in the fields of medicine (cardiology), biomedicine, physiology and pharmacology and biochemistry were contacted by e-mail with a link to a questionnaire, which they could immediately fill out without registration or entering identification data, completely anonymously.

Before the questioning, the experts were briefly introduced to the issue, the results of animal studies to date, and an overview of the proposed technology according to information from previous chapters. Subsequently, there is an explanation of the elicitation method and an explanation of how the expert can express his opinion.

Experts were invited to give numerical answers or to choose one from possible answers. Experts could also leave comments and notes on each question. Each of the experts had an assigned weight. This weight balanced the expert's answer to the main question, the aim of which was to find out by what percentage the incidence of rVF during PCI of STEMI-patients is potentially reduced if melatonin (4 mg/kg) is administered intravenously before/during PCI as an antiarrhythmic treatment for patients with a predicted high risk of rVF.

To obtain a summary of the predicted medication efficacy value that could subsequently be used in a model for eHTA of the new technology, the expert's weighted responses were averaged.

The method of evaluation of experts' weights was analogous to that used in the work of Ivlev et al. [37], where the authors dealt with the weighting of expert opinions in the context of health technology assessment. According to the authors, the weight of the expert's opinion was determined by evaluating the expert's overall experience, current position, level of education, experience with research issues, and the level of expert participation in the problem [37, 38].

Experts had the option of choosing from 4 possible answers to each of the 5 questions (Table 2). With a weighted sum of points (according to Equation 1), they got a score that had been used to weight their answers in the elicitation process [37].

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$$w_T = \frac{1}{n}\sum_{i=1}^{n} w_i, \quad (1)$$

where
w_T is total score
n is number of criteria
w_i are points for individual criteria

Experts were also asked questions whether they consider a dosage of melatonin 4 mg/kg to be appropriate. Experts were invited to supplement their answers with a comment or a proposal to change the dosage. Questions were also asked about the severity of side effects of the chosen dosage and the assessment of whether the benefits seem to outweigh the risks associated with the new proposed treatment procedure. The severity of adverse effects was assessed using the CTCAE v5.0 scale. Answers to multiple-choice questions were presented graphically.

Table 2: Criteria for weighing of expert opinions [37].

Total work experience (years)	Points	Job position	Points	Education	Points	Experience with the issue (years)	Points	Level of participation in the problem	Points
> 10	1	Head of organization	1	Ph.D.	1	> 10	1	Experts specialize in the given issue	1
5–10	0.8	Deputy head	0.8	M.D.	0.8	5–10	0.8	Experts participate in practical work to solve the problem, but the issue does not fall into his stated specialization	0.8
< 5	0.6	Head of department	0.6	Ing. / M.Sc.	0.6	< 5	0.6	Issue falls within expert's specialization	0.6
0	0	Deputy head of department	0.4	less	0	0	0	Issue does not fall under expert's specialization	0.3

Results

Ten experts participated in the elicitation and fully completed the questionnaires. Their responses on expertise and knowledge were evaluated to assign weights (see Fig. 1).

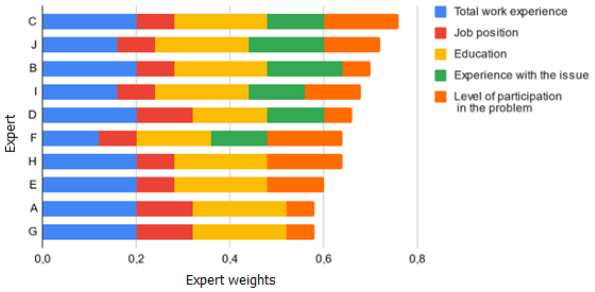

Fig. 1: Expert weights compiled from points according to individual criteria.

The results of the experts' answers (Fig. 2) to the main research question were weighted and statistically processed to obtain a result that can be used in model within the eHTA. Predicted effectiveness of the medication is 71.82%. So, if the therapy works as expected, rVF will not occur in 71.82% of STEMI patients in whom this complication would otherwise occur during PCI.

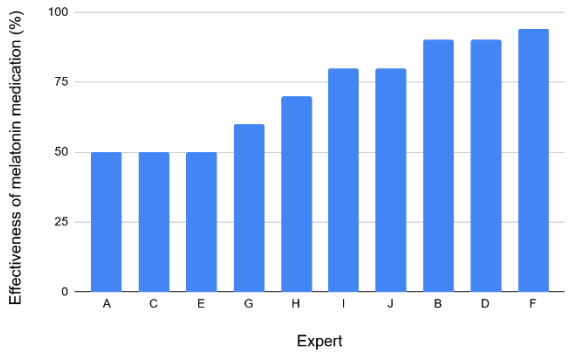

Fig. 2: Expert's opinions obtained through elicitation about potential effectiveness of melatonin medication in STEMI patients with predicted high risk of rVF during PCI.

When asked about the appropriateness of the expected dosage of melatonin, 80% of the experts answered that it was appropriate. Two experts who disagreed did not add a dose proposal or comments.

Most experts (80%) agreed that the expected dosage can cause adverse effects Grade 1 (according CTCAE v5.0 scale)—Mild; asymptomatic or mild symptoms;

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clinical or diagnostic observations only; intervention not indicated. Two experts think that adverse effects can reach Grade 2—Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living).

Fig. 3 shows the distribution of experts' responses about the risk-benefit ratio of the proposed melatonin treatment (4 mg/kg) in STEMI patients identified as being at high risk of rVF during PCI.

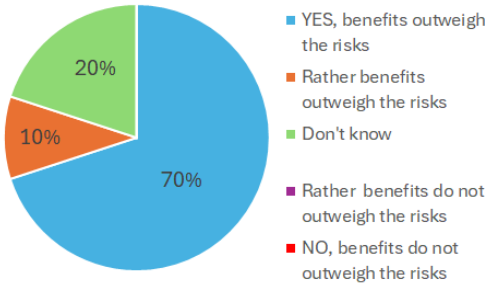

Fig. 3: Expert opinions about the risk-benefit ratio associated with the administration of melatonin 4 mg/kg before/during PCI as an antiarrhythmic for STEMI patients with detected high risk of rVF.

Discussion

The main objective of the study was to determine the expected efficacy of rVF-protective therapy using i.v. melatonin (4 mg/kg) in STEMI patients undergoing PCI, whom were diagnosed by new technology with a high risk of reperfusion ventricular fibrillation using the new technology, using the elicitation method within the framework of eHTA. Ten experts participated in the elicitation. They were familiar with the results of animal experiments and expressed their opinions on what effect the proposed rVF-protective medication would have on STEMI patients with diagnosed high risk of rVF during PCI. Numerical answers to the main question were weighted with point scores according to the experience of experts. The result is an effectiveness value of 71.82%, which is comparable to the published results of animal experiments, where the mean efficiency value was 70% [6–9]. This mean value of antiarrhythmic efficiency of melatonin treatment from animal experiments was not communicated to the experts during training before the elicitation process in order to eliminate the influence on their private opinion.

In a ratio of 8 out of 10 experts recognized the proposed melatonin dosage as appropriate. The two experts who disagreed with the dosage did not submit their proposals for its change and did not comment on their opinion in any way. The majority (80%) of experts also agree that the proposed melatonin dosage may cause only Grade 1 Mild side effects; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Answers to the question about risk-benefit ratio of proposed rVF-protective medication showed some uncertainty among experts. Two experts answered that they couldn't judge the ratio, and another one leaned towards that benefits outweighing, but was not sure. The other seven experts responded that benefits clearly outweigh the risks.

Although elicitation is the least described area of eHTA and there is generally no uniform eHTA methodology, elicitation has its irreplaceable potential for the correct creation of a new technology model within the framework of early evaluation [35, 39–42]. This research is part of eHTA of new diagnostic technology in cardiology and deals with finding an unknown parameter of the model, specifically the potential effectiveness of rVF-protective medication. Intravenous administration of melatonin 4 mg/kg before/during PCI was chosen as a potential medication for patients with detected by the new technology high risk of rVF. Its rVF-protective effectiveness has been tested mainly in animal experiments, but there are assumptions that the origin, causes, pathophysiology and electrophysiological characteristics of rVF in animals and humans are comparable [30].

Further work on the project will build on the obtained results of expert elicitation and our cellular studies. A previously unknown parameter obtained as part of this research, which includes melatonin direct effect on myocytes, will be added to the prepared model of the new healthcare technology. A comprehensive eHTA will be performed to further evaluate the integration of melatonin as an rVF-protection medication within the context of PCI for STEMI patients at high risk of rVF.

Limitations

A certain limitation of the study is the innovative approach to rVF-protection using melatonin. Probably, more accurate results could have been obtained if the medication had at least undergone basic clinical trials, but this process, in connection with extensive legislative requirements, can take a long time and be associated with great costs.

Among other possible limitations, it is worth mentioning that 4 out of 10 experts admitted in the questions about determining the weight of expert opinion that they lack experience with the given problem based on their specialization. However, the chosen methodology assumes this possibility and all experts contacted were carefully selected based on their specialization, education and practice.

Conclusion

Early stage HTA has great potential for manufacturers in the current legislation and market conditions, but it has its specificities because it is carried out in the state

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of incompleteness of the design and development of the technology. Our results show that elicitation is a useful and easy-to-implement method for supplementing the unknown parameters of eHTA models. Achieved results are relevant and applicable within the framework of the planned eHTA, and used elicitation methodology is general and could applied in the context of similar eHTA research of other health technologies.

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