ผลของการได้รับการรักษาล่าช้าของผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลัน: การทบทวนวรรณกรรมอย่างเป็นระบบ

The effect of delaying treatment among acute myocardial infarction patients: A systematic review

บทความวิจัย
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บทคัดย่อ

กล้ามเนื้อหัวใจตายเฉียบพลันเป็นสาเหตุสำคัญของการเสียชีวิตของผู้ป่วยทั่วโลก ผู้ป่วยจำนวนมากที่ได้รับการรักษาล่าช้าจะประสบกับอาการไม่พึงประสงค์และภาวะแทรกซ้อนต่าง ๆ อย่างไรก็ตาม ยังไม่มีการศึกษาและรวบรวมว่าอาการไม่พึงประสงค์หรือภาวะแทรกซ้อนจากการได้รับการรักษาล่าช้าประกอบด้วยอะไรบ้าง และมีความแตกต่างกันอย่างไรระหว่างผู้ที่ได้รับการรักษาล่าช้าและผู้ที่ได้รับการรักษาทันเวลา การทบทวนวรรณกรรมอย่างเป็นระบบครั้งนี้จึงมีวัตถุประสงค์เพื่อทำการรวบรวมและสรุปผลของการได้รับการรักษาล่าช้าของผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลัน ผู้วิจัยทำการสืบค้นงานวิจัยจาก 5 ฐานข้อมูล ได้รายงานการวิจัยทั้งสิ้น 35 เรื่อง นิยามของการได้รับการรักษาล่าช้า ได้แก่ การได้รับการรักษาหลังมีอาการ 1, 2, 3, 6, และ 12 ชั่วโมง ส่วนใหญ่ทำการศึกษาการได้รับการรักษาล่าช้าในระยะก่อนเข้ารับการรักษาในโรงพยาบาล ถึงแม้ว่านักวิจัยจะรายงานผลการศึกษาที่ขัดแย้งกันแต่การศึกษาส่วนใหญ่รายงานว่า การได้รับการรักษาล่าช้ามีความสัมพันธ์กับการตรวจพบคลื่นเอสทียกและคลื่นคิว ประสิทธิภาพการทำงานของหัวใจลดลง การเพิ่มขึ้นของเอนไซม์กล้ามเนื้อหัวใจ จำนวนของภาวะแทรกซ้อน ระดับความปวดและความวิตกกังวลสูง ระยะเวลาการนอนในโรงพยาบาลนาน ค่ารักษาสูง การเกษียณจากงานเร็ว และอัตราการตายสูง การศึกษาครั้งต่อไปควรทำการวิเคราะห์เมทต้าเพื่อให้สามารถตัดสินผลจากการได้รับการรักษาล่าช้าได้ชัดเจนยิ่งขึ้น นอกจากนี้ การทบทวนวรรณกรรมอย่างเป็นระบบเกี่ยวกับโปรแกรมที่ช่วยลดระยะเวลาในการได้รับการรักษายังเป็นหัวข้อที่สำคัญที่จะช่วยให้สามารถค้นหาโปรแกรมที่เหมาะสมในการจัดการกับปัญหาการได้รับการรักษาล่าช้าในผู้ป่วยกลุ่มดังกล่าว

คำสำคัญ: การรักษาล่าช้า กล้ามเนื้อหัวใจตายเฉียบพลัน อัตราการตาย ผลลัพธ์ที่แย่ลง

Abstract

Acute myocardial infarction (AMI) is a major cause of death for patients around the world. Many patients who delay treatment often experience negative outcomes. However, there is so much we do not know about what negative outcomes are and how they difference between the groups that did delay and did not delay treatment, a systematic review is needed. This systematic review evaluated the effect of delaying treatment among AMI patients by searching on five data bases. Thirty five empirical articles were accepted for this review. The definitions of delay treatment were 1, 2, 3, 6, and 12 hours to receive treatment after

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symptom onset. Almost every researcher studied in the pre-hospital phase. Although the researchers reported contrasting research findings, almost every study reported that delaying treatment was associated with STEMI, Q-wave MI, cardiac dysfunction, cardiac enzyme elevation, a number of complications, high level of pain and anxiety, long length of stay, high cost, early retirement, and high mortality rate. Meta-analysis is needed to determine the effects of delaying treatment. Intervention to decrease time to get treatment is an important topic for the next review to determine appropriate interventions shorten time to treatment.

keywords: treatment delay, acute myocardial infarction, mortality, worse outcomes

Introduction

Acute myocardial infarction is the major cause of death for patients around the world.[1] American Heart Association reported that AMI causes a high admission rate, high complication rate, high mortality rate, and high cost of treatment for patients.[1] AMI patients suffer from cardiac events every 26 seconds and of those patients, one dies every 90 seconds from a heart attack.[1] Moreover, 38 % of patients who experience heart attack symptoms will die within one year, and delaying response was a major cause of death.[2] High mortality rate of AMI patient was found two hours after experiencing AMI symptoms with about six out of 10 patients died before arriving at the hospital.[3,4] Moreover, AMI patients who survive and arrive at the hospital have many complications, and these complications need advanced treatment and long hospital stay.[5,6]

Because the heart muscle can tolerate an ischemic condition for only two hours, patients who take longer to receive treatment have more negative effects than patients who receive treatment on time.[7] AMI treatments and procedures can be effective when the patient receives them within two hours—this is called the *golden period*.[7,8] When a coronary artery is obstructed by an embolism or clot, the heart muscle will experience ischemia. If this process continues, the heart muscle will be destroyed (injury) and cannot recover (infarction).[1] This is a reason why patients have to go to hospital and receive treatment within two hours.

Factors associated with delaying treatment is an area of growing research interest.[9,10,11] It is true that so many researchers exploring factors related to delay treatment, and the systematic reviews were already conducted to determine what factors related to this phenomenon.[12] However, there is so much we do not know about what negative outcomes are and how they difference between the groups that did delay and did not delay treatment. Moreover, some studies reported different negative outcomes, so a systematic review is needed. A universal delay and effect of delay in treatment needs to be established by a systematic review to foster research in this area.

Objective

To review the definition of delaying treatment and the effects of delaying treatment among AMI patients by reviewing empirical articles.

Methods

We conducted this review by following the framework of comprehensive searching and the integrative review created by Whittemore and

Knafl.[13] The following steps were undertaken: identifying problem, searching literature, evaluating data, analyzing data, comparing and contrasting data, presenting data, and discussing review findings.

The search was conducted in five databases: Medline, CINHAL, PsychInfo, SCOPUS, and Ageline and keywords were provided. We put these terms together with OR: "delay decision," "health seeking behavior," "prolong pre-hospital," "pre-hospital delay," "care seeking," "help seeking," "timely treatment." Then we added AND those keywords to our cardiac terms: "chest pain," "angina," "acute coronary syndrome," "heart attack," "myocardial infarction," "ST-elevation MI," "STEMI," "cardiac event." Finally, we used AND those two searches to our outcome terms: "effect," "impact," "result,""outcome." Inclusion criteria were: Studies published 1988 to 2016 on AMI or acute coronary syndrome or heart attack, report effect of delaying treatment, and published in English. Exclusion criteria were: study published only abstract for the conference, included uncompleted results, and could not find the original full paper.

After finishing the searching processes, the two researchers independently reviewed title and abstract. Then the two reviewers reached consensus to identify which study related to the review topic. If the two reviewers did not agree with each other, the third reviewer did the final judgment. Independent review was also applied for the full paper review.

Results

We retrieved 17,853 articles from the five databases and 75 articles from hand searching (Figure 1). This review includes all age groups for research study. Based on the criteria, we reviewed full paper for 146 articles and only six articles directly studied the effects of delaying treatment. While the rest of them, 140 articles, focused on factors associated with delaying treatment. Of these, 29 studies were a minor focus on the effect of delay. Finally, 35 articles were included for this review.

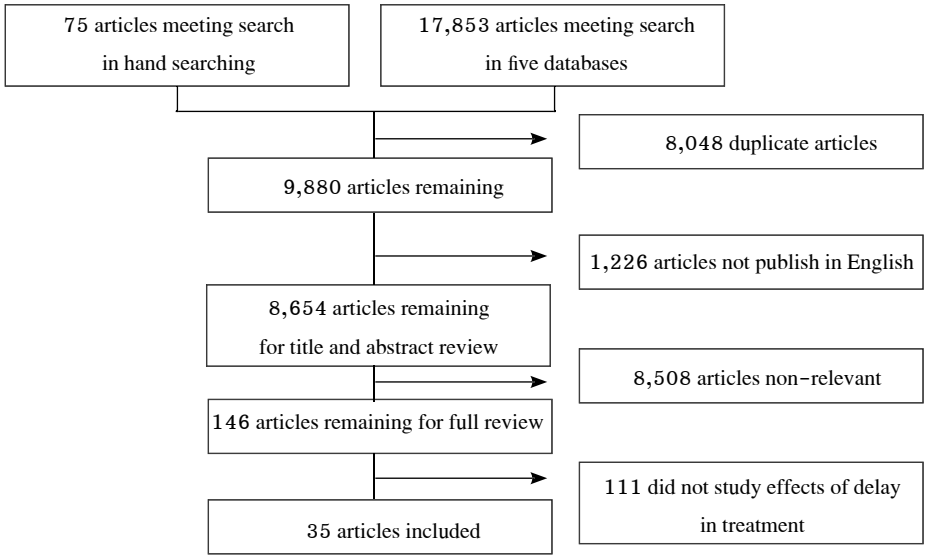

Figure 1: Flow chart of the review process.

The Studies Description

Five articles were published in 2006, three in 2005, 2008 and 2014, and two in 1997, 1999, 2010, 2012, and 2013, with one each in the left year. Almost every study was published as a research article (34), only one was a dissertation. Sixteen were studied by using cohort study and nine articles were cross sectional studies. Sixteen of the articles were studied in United States of America, two articles were studied in Germany, Netherland, and Sweden, and one article each was studied in Italy, Canada, Greece, Thailand, Poland, England, New Zealand, International settings, Japan, Portugal, China, the United States and Australia, and Denmark. Almost all articles were studied in mixed age groups (adults and older adults), but the mean ages of each study were higher than 60 years old. There were only 15 studies reporting the measurement for their studies and all of them were developed from the principal researchers. However, only four articles reported the psychometric of their measurements. Unfortunately, one researcher reported that the psychometric of measurement was good (accepted), but did not report the value of psychomestric[14].

Definition of Delaying Treatment

Delaying treatment was defined differently in 35 studies. Basically, times of delaying treatment were defined into two groups: receiving treatment one and two hours after experience the first heart attack symptom for non-intervention studies, such as factors related to delay treatment; and three, six, or twelve hours for intervention studies, such as delaying treatment of catheterization procedures or thrombolytic drugs. Based on this review, there were three studies did not report the definition of delaying treatment.[4,15,16] Twelve studies defined delaying treatment by using one hour receiving treatment after experiencing the first symptom of heart attack[17-28], ten studies used two hours[14,29,30,31-37], four used three hours[38-41], four used 12 hours[42-45], one used six hours[46], and one used both one and two hours[6].

Phase of Delaying Treatment in AMI Patients

Treatment delays can be sorted into three phases. *The patient's recognition action phase* is the duration of time between the time when patients experience AMI symptoms until they decide to seek treatment.[29,47] *The pre-hospital action phase (transportation)* begins after AMI patients ask for help or call an Emergency Medical Service (EMS) until they arrive at the hospital.[29,48] *The hospital action phase* is the interval when AMI patients arrive at the hospital until they receive the AMI treatment methods, called door-to-needle or balloon.[1,29]

For this review, we found that the 35 studies included the patient's recognition action phase and transportation phase into the pre-hospital phase, and still had the hospital phase for the studies. There were 20 articles that focused on the pre-hospital phase, in contrast, 15 articles studied the delaying hospital phase.

In cases of level of delaying treatment, the researchers for 35 studies divided their participants into a variety of sub-groups. Some studies calculated only the total time of delaying treatment as continuing variable (how many minutes delayed), but some studies divided time (level of delaying treatment) into categorical variables including 0-30,31-60, 61-90, 91-120, 121-360 minutes; shorter than

two hours and longer than two hours; shorter than three hours and longer than three hours; less than two hours, two to four hours, four to six hours, and longer than six hours; less than three hours, three to 12 hours, and longer than 12 hour; less than one hour, one hour, one to two hours, 2.1 to three hours, 3.1 to four hours, 4.1 to five hours, 5.1 to six hours, 6.1 to eight hours, 8.1 to 12 hours, and longer than 12 hours. Finally, one study divided time of delaying treatment by using quartiles.

The Effects of Delaying Treatment in AMI Patients

The effects of delaying treatment can be categorized into eight domains to describe the effects of AMI when patients delayed treatment. There were electrocardiogram changes, heart function and cardiac enzyme changes, physical complications, mental effects, length of stay, cost, work retirement, and mortality rates.

Electrocardiogram (EKG) Changes

This review showed that there were 13 out of 35 studies focusing on EKG changes. The types of EKG that were studied including ST-segment elevation myocardial infarction (STEMI), non ST-segment elevation myocardial infarction (NSTEMI), Q-wave myocardial infarction, and non Q-wave myocardial infarction. Six out of nine studies found that delaying treatment caused STEMI[15,22,30,34,35,40], but three studies reported non-statistical significant differences in patients who did delay versus those who did not delay treatment[16,29,45]. Five studies examined NSTEMI but only one study reported statistically significant differences between both groups.[15] Four studies explored non-Q-wave MI but they did not find statistical significance in both groups.[14,16,31,35] Finally, three out of five studies found that statistics showed significant differences in Q-wave MI between patients who delayed and did not delay treatment[14,36,38].

Heart Function and Cardiac Enzyme Changes

Nine studies examined these variables and in five studies found statistical significance in terms of ejection fraction and cardiac enzyme levels in patients who delayed and did not delay treatment[4,17,27,29,39]. AMI patients who delayed treatment had decreased percentages of blood leaving the heart each time it contracted (ejection fraction) and increased in cardiac enzyme on blood circulation. However, four studies found no difference between the groups[14,26,41,42].

Physical complications

Physical complications of heart attack included arrhythmia, re-infarction, recurrent ischemia, cardiogenic shock, congestive heart failure (CHF), stroke, and measuring number of various complications. In the case of stroke, it was a complication after patients delayed treatment (indirect effect from delaying treatment). There were only three studies that examined arrhythmia, and two studies reported statistically significant differences between both group[4,24], but one team reported in contrast[26]. Six studies examined re-infarction, but there were only two studies reporting statistically significant differences in both groups.[42,44] Six studies compared the recurrent ischemia, but only one study reported statistically significant differences between two groups.[42] Eight studies examined cardiogenic shock, but only three studies reported statistically significant differences between two of them.[21,33,36] Seven out of twelve studies reported statistically

significant differences in incidence of CHF between two groups.[4,21,24,26,33,34,36]

Patients who delayed treatment received late thrombolytic drugs and cardiac intervention, and it caused strokes for these patients. Four out of five studies reported statistically significant differences in incidence rates of stroke between two groups.[21,24,33,44] Finally, six studies compared the number of complications in patients who delayed and did not delay treatment; in five out of six reported, delaying treatment caused numerous complications than those who did not delay[6,20,25,34,38].

Level of Pain, Fear, and Anxiety

There were only two studies comparing pain levels, and fear/anxiety between patients who delayed and did not delay treatment. One team reported fear/anxiety differences in patients who delayed.[26]Yet, the other studies reported that patients who delayed and did not delay did not have different pain levels[29]. However, both groups did not point out that delay treatment caused high level of pain or level of pain caused delaying treatment.

Hospital Length of Stay

Length of hospital stay was defined as the number of days or the duration of living in the hospital for heart attack or treatment of complications. Two out of three studies reported that patients who delay treatment had longer hospital length of stays than patients who did not delay.[24,26] Another study found contrast findings[43].

Treatment Cost

The two studies found that patients who delayed treatment had higher costs for the treatment of a heart attack and its complications than the patients who did not delay treatment[6,25].

Returning to Work and Work Retirement

One study examined the effects of delaying treatment on working status. The study found that AMI patients who delayed treatment over two hours had lower rate of returning to labor market (back to work) when comparing with patients who get treatment shorter than two hours. Moreover, longer time delaying treatment was also associated to earlier retirement from work. AMI patients who delayed receiving treatment reported higher rate of early retirement than patients who did not delay.[37]

Mortality rates

Mortality rate was the most important variable that the researchers used to determine the effects of delaying treatment. Based on this review, there were 28 studies paid attention on mortality rate. The mortality was divided into three sub-groups: in-hospital mortality rate, mortality rate 30 days after discharge, and mortality rate one year after discharge. However, the in-hospital mortality rate was more often use in these studies. There were 23 studies reported a higher mortality rate among those who delayed than patients who did not delay when they experienced heart attack symptoms. [4,6,17,21,30,23,25,27,28,32,33,35,36,38,41,42,44,46]

Discussion

For definition of delaying treatment, most studies shared a common factor, the golden period, —in which receiving treatment within two hours after a patient first experiences heart attack symptoms, although definitions varied by the number of hours. Based on this review, five definitions of delaying treatment were reported. Delaying treatment was defined as receiving treatment one, two, three, six,

and twelve hours after a patient first experiences heart attack symptoms. There were two possible reasons for these various cut-off-points: 1) evidence of treatment changed based on time and 2) kinds of AMI treatments or procedures that the researchers applied for their studies. The definitions of delaying treatment vary with the time period of each study (between 1998 to 2016) and the golden period of each treatment procedure. In the past, the golden period of thrombolytic therapy was receiving thrombolytic drugs within six or 12 hours. In the same way with cardiac procedures, heart attack patients received cardiac intervention within six or 12 hours.[49]However, the golden period of thrombolytic therapy and Percutaneous Transluminal Coronary Angioplasty (PTCA) such as balloon and stent, has changed from six or 12 hours to within two hours because many research studies showed evidence of time associated with effectiveness of cardiac interventions.[1,24,41-43]The American Heart Association (AHA) point out that "time is muscle," meaning the percentage of heart muscle damage is depending on time, so the AHA strongly recommend that receiving treatment faster causes better outcomes. These are reasons why the 35 studies applied different cut-off-points to define a treatment delay.

Delaying treatment occurs in three phases: patient recognition phase, transportation phase, and hospital action phase. Researchers have focused on different phases of delaying treatment because they have different aims for their studies. The researcher studied in the pre-hospital phase because of the concern that the pre-hospital phase was the main problem of delaying treatment and caused negative outcomes for heart attack patients.[39,50] Moreover, they wanted to determine factors that may be associated with delaying treatment in the pre-hospital phase.[39] In cases of studying hospital phase, the researchers wanted to know how many patients who delayed receiving cardiac treatments and procedures in different timeframes got better or worse. The results from the hospital phase's studies could determine the most appropriate period of time that AMI patients should receive each treatment or procedure. This is the same reason we found from other reviews why the studies focused different phases of delay.[51,52] Beckley[51] and Bird, Woods, and Warren[52] who did systematic reviews also found that many studies paid attention on different phases of delay to identify the specific delayed factors for each phase[51,52].

Inconsistency of definition for delaying treatment and when we should start counting time until patient arriving at hospital have challenged our ability to compare findings across studies. Various cut-off-points used in the studies for our reviews has caused conflicting results. El-Masri and Fox-Wasylyshyn found that the results of delaying treatment were different when using different cut-off-point, although, using the same data set.[53]Mackay reported that not only using different cut-off-point causing different results, but also the time when started counting (symptom onset) until patients arriving at the hospital still was a problem.[48] Developing and validating a definition of symptom onset is needed. This will increase clarity and confidence in the comparisons and conclusions between various studies.

There are three stages of cardiac muscle damage associated with EKG changes: ischemic, injury, and infarction.[1]In AMI situation and without therapeutic intervention, the EKG typically pro-

gresses from presenting with hyper-acute T waves, ST-segment elevation, abnormal Q waves, T-wave inversion, and becoming normalization of the ST segment again.[54,55]The researchers reported conflict research findings in case of STEMI and O-wave MI. This contradiction may be caused by different definitions, based on time frame in the delaying treatment. However, long time damages and large infarction sizes were associated with EKG change, almost every researcher found that AMI patients who delayed treatment often showed STEMI and Q-wave MI.[22,54,55]

Cardiac enzymes including Troponin-T, and CK-MB released from myocardial cells into the blood when cardiac muscle is damaged.[1,29] Because delaying treatment associated with heart muscle damage, AMI patients who spent longer time to seek treatment showed higher level of cardiac enzyme.[4]In the same way, ejection fraction decreased when there is a decrease in the heart's pumping because of cardiac muscle damage.[41]The longer waiting time patients spent, the larger area of cardiac muscle damaged. Patients who spent a long time to get treatment showed higher levels of cardiac enzyme and lower percentages of blood leaving the heart each time it contracted (ejection fraction) than patients who did not delay.[20,39]

Hofgren et al. and Guerchicoff et al. reported that delay in treatment were associated with losing blood and oxygen supply, then low cardiac function was caused.[4,41] Moreover, this situation caused many complications, such as CHF, ventricular fibrillation, hypotension, pericarditis, and death.[1]The complications may occur in not only heart function such as arrhythmia, re-infarction, recurrent ischemia, and cardiogenic shock, but also lung function and kidney function.[26,36] Patients who progress to cardiac muscle damage can have more severe and higher number of complications.[18,43]

Stroke is an indirect effect of delaying treatment of heart attack. It was a complication of late treatment after patients delayed revascularization as defining as thrombolytic therapy and primary percutaneous transluminal coronary angioplasty (PTCA). The delay in revascularization of heart attack patients influences risk of ischemic stroke[56]. De Graaff at al. found that delaying of thrombolytic therapy (delay time of door to needle) and late PTCA (delay time of door to balloon) were associated to high rate of ischemic stroke.[56] In contrast, heart attack patients who received thrombolytic therapy within 15 minutes and PTCA within 90 minutes were associated with a lower risk of ischemic stroke.[56] This is a reason why heart attack patients who delayed treatment experienced high prevalence rate of stroke

Many studies showed that the level of anxiety/fear in patients who delayed and did not delay treatment were different. However, such studies did not conclude that patients who had a high level of anxiety/fear came early to the hospital, or patients who were delaying treatment had a higher level of anxiety/fear.[26]Either can occur. Nevertheless, this review found that pain levels did not produce statistically significant differences between two groups because age may affect the level of pain. Increasing age cause low sensation of pain, especially the tolerance toward deep pain sensation was decreased because of older age.[4]Almost participants for this review were older than 60 years, and researcher reported no pain in older adult with AMI.[29]

Patients who delaying treatment experienced a more severe and higher number of complications.[20,34,38] Therefore, it is not surprising that they spent a longer time in the hospital than patients who arrived early in the emergency department. In the same way, patients who experienced many complications, higher severity of complications, and longer lengths of stay, resulting in more money spent for their treatments and procedures.[6,8,57]

Finally, the studies compared the mortality rate between patients who delayed and did not delay treatment. According to the evidence, duration of time using to get treatment is associated with areas of cardiac muscle damage and severity and number of complications, so patients who delay treatment had higher mortality rates than patients who did not delay.[6,23,43]This finding was reaffirmed by other studies in the past 20 years, and we have found the same results.[4,23]Studies found that when cardiac muscles lose oxygen and blood supply for longer than 30 minutes, infarction occurs. Unless blood supply returns in two hours or longer, the infarction area cannot recover.[22,43] When the cardiac muscle loses the ability to effectively pump, other vital organs such as kidneys and liver were failed, causing a coma.[15,43] Because of the time associated with cardiac and vital organ complications, patients who delay treatment had experienced higher mortality rates.

Conclusion

Delaying treatment in AMI patients remains a major problem for patients around the world. Time to treatment is associated with treatment effectiveness, so patients who miss the therapeutic window of opportunity (golden period) do not experience the positive outcomes. A reviewed on 35 empirical articles demonstrated that the effects of delaying treatment, including EKG change, cardiac dysfunction and high level of cardiac enzymes, physical complications, anxiety and level of pain, length of stay, cost, work retirement, and mortality rate. Although contrasting findings were reported, almost every study showed that delaying treatment was associated with STEMI, Q-wave MI, low cardiac dysfunction, cardiac enzyme elevation, a number of complications, high level of pain and anxiety, long length of stay, high cost, early retirement, and high mortality rate. This review supported that the more patients spent time to get treatment, the more they suffered from negative effects from heart attack.

Limitation of published studies

Some studies used convenience sampling methods, so it might cause selection biases. In the same way, some studies collected data by using the medical record, which might be associated with information bias. Finally, the 35 studies defined the terms of delaying treatment in a variety of timeframes (one, two, three, six, or twelve hours), so this may affect research findings and our ability to provide conclusion across 35 studies was limited.

Recommendations

For future study, a meta-analysis method should be used to determine the effect of delaying treatment by pooling data from many studies together. Specific study both in the effect of delaying treatment and older adults will be needed for the future research. Finally, the systematic review for intervention to decrease time to get treatment is the

most important topic to determine effective intervention to shorten waiting time.

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