INDUCED HYPOTHERMIA AND ITS EFFECTS ON CARDIAC ARRHYTHMIAS

by

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Abstract

The purpose of this integrated review of the literature was to determine the relationship between therapeutic hypothermia and cardiac arrhythmias. The reviewed literatures were English based articles from year 2003-2013. Relevant information from the American Heart Association and the International Liaison Committee on Resuscitation was used to further enhance research results. The results of this literature review showed hypothermia treatment propensity to prolong QT interval without precipitating life-threatening arrhythmias. Although arrhythmias can be potentially increased under induced hypothermia, it has been shown that treatment is easier while under hypothermic conditions. The reviewed research also shows that hypothermia treatment should be expanded to include more circumstance besides ventricular cardiac arrest. It was suggested that the reason for lack of use of hypothermia treatment under the suggested conditions was due to the restricted circumstances in which it is suggested to be used. Other recommendations include increased monitoring for cardiac rhythms during cardiac arrhythmias and protocols for arrhythmia treatment.

Dedications

To all those that believe in me.

Acknowledgements

I would like to thank all the members of my committee, Dr. Paul Desmarais, Dr. John Decker, and Dr. H. Edward Fouty Jr. I would also like to thank Dr. Leslee D'Amato-Kubiet for her guidance.

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Contents

Introduction

Induced Hypothermia

Medically induced hypothermia, as it relates to cardiac arrest, is the cooling of the core body temperature to 32-34° C (89.6-93.2° F) (Holden & Makic, 2006). There are three recognized stages of hypothermia: mild, moderate and severe. Mild hypothermia is from 33-35° C (91.4-95° F), moderate from 28-32° C (82.4-89.6° F) and severe < 28° C (82.4° F). The therapeutic range is within the mild to moderate levels (Holden & Makic, 2006).

The use of hypothermia in cardiac arrest patients has been documented since the late 1950's (Polderman, 2008). Although successful, it was subsequently abandoned due to uncertain benefits and difficulties with its use. As providers have grown better able to manage therapeutic hypothermia, it has emerged as an important therapy following cardiac arrest by increasing survivability and offering neuroprotectition (Mooney et al., 2011).

Hypothermia treatment is not without adverse effects. Hypothermia treatment has been shown to cause various cardiac arrhythmias including QT prolongations, and bradycardia due to the decrease in oxygen demands in response to lower temperatures. There is also evidence that therapeutic hypothermia increases the risk of infection and coagulopathy (Storm et al., 2011).

Hypothermia is thought to reduce tissue injury by reducing metabolic need, ATP preservation, and has even shown a positive effect on myocardial contractility. By reducing metabolism, mild hypothermia is believed to suppress injuries associated with reperfusion injury. Some of these injuries include calcium shifts, free radical production, and apoptosis (Nolan et al., 2003).

Hypothermia treatment has also been shown to reduce infarct size when administered prior to return of spontaneous perfusion (Götberg, Olivecrona, Götberg, Koul, & Erlinge, 2010).

Hypothermia treatment has also shown positive effects in neurological outcomes of cardiac arrest patients. Hypothermia reduces cerebral metabolic demand by 6% for every 1℃ reduction in body temperature.

Hypothermia treatment must be carefully implemented due to the potential for adverse effects. Hypothermia is thought to decrease the depolarization of pacemaker cells thereby extending the duration of action potentials. The most common electrocardiograpic changes were the prolongation of the PR and QT intervals and the widening of the QRS complex.

Induced hypothermia has also shown to increase the presence of Osborn waves, which have been associated with ventricular ectopy (Bell, 2010). The hypothermic cooling process has been shown to correlate with a decrease in potassium levels, which is thought to potentiate the arrhythmias; polymorphic ventricular tachycardia (PVT) shows the strongest association with hypokalemia (Mirzoyev, McLeod, Bunch, Bell, & White, 2010).

Cardiac Arrhythmias

Hypothermia treatment has a strong association with cardiac arrhythmias. Ventricular arrhythmias are a major cause of death in hospitalized patients post cardiac arrest (Mirzoyev et al., 2010). QT prolongations themselves have been shown to induce malignant arrhythmias such as ventricular tachycardia. However, elongations of QT intervals are easier to treat while under hypothermic conditions (Storm et al., 2011).

In 2009, Tiainen et al. stated that hypothermia treatment did not have a clinically significant impact on arrhythmias. They claimed that heart rate could be an indicator of a favorable outcome. Hypothermic cardiac arrhythmias could also be caused by other life saving measures such as medications. Hypothermic treatment can increase the effects of drugs and further prolong QT intervals to potentially dangerous degrees.

Problem

Therapeutic hypothermia has been linked to favorable outcomes for post cardiac arrest victims. Medically induced hypothermia is also thought to offer protective mechanisms in cardiogenic shock patients (Götberg et al., 2010). Close cardiac monitoring is needed due to the potential for cardiac arrhythmias especially if the patient is treated with medications that can further prolong QT intervals. Healthcare awareness of the potential for dangerous arrhythmias affects treatment during and post induced hypothermia.

Hypothermic treatment has been endorsed by the International Liaison Committee on Resuscitation; therefore, its use has become increasingly widespread. With the widespread use of a potentially beneficial treatment, healthcare has the moral and ethical obligation to know and prepare for potential adverse effects. Although there is moderate knowledge about the potential for cardiac arrhythmias, there is no comprehensive action plan to treat these occurrences. It is not only important to know that adverse effects can happen, but it is also important to have protocols in place for such events.

With the increasing demand on the healthcare system due to the influx of newly insured individuals, it has become even more important to eliminate potential problems before they occur. Not only is it important for patients, but it is also the economically responsible thing to do. With limited resources and a potential influx of patients, it is more important than ever to streamline protocols using the newest and most efficient evidence based practices. Examining the current literature on induced hypothermia and cardiac arrhythmias is instrumental in the adoption of protocols within the health care facility.

As healthcare participants and patient advocates, nurses are responsible for providing assessments vital to preventing malignant cardiac arrhythmias. It is imperative that nurses know

how to treat and prevent possible arrhythmias. A knowledgeable nursing staff is at the forefront of safety and positive patient outcomes. Understanding what adverse effects are possible, and the potentiating factors that can cause them, is crucial in limiting harmful outcomes. Because medically induced hypothermia is such a new mode of therapy, there is, currently, a lack of knowledge as it relates to complications, protocols, and treatment in this area. Current literature endeavors to fill these voids but no standard protocols have been established.

Purpose

The ambition of this integrated review is to provide a comprehensive analysis of the research on therapeutic hypothermia and its correlation with cardiac arrhythmias. An examination of the various levels of hypothermia and the adverse effects shown at each specific level will be analyzed. This analysis will look for clinically significant findings. The literature reviewed will provide insight to understanding various therapeutic hypothermia protocols. This thesis will provide supplementary understanding of nursing related care for cardiac patients given hypothermic treatment. The goal of this review is to positively impact nursing and patient management by suggesting protocols that may be used in the care of patients undergoing therapeutic hypothermia.

Method

An examination of current research related to therapeutic hypothermia in cardiac patients was conducted. Animal studies were included in the synthesis of research articles. An interdisciplinary literature review search was completed using CINAHL, pubMED, and medline. Inclusion conditions included peer reviewed, full text, and English language articles between the years of 2003 and 2013. The search parameters were limited to those which included medically induced hypothermia, cardiac patients, encouraging effects, and adverse effects.

Background

Therapeutic hypothermia treatment has been highly praised for its neuroprotective abilities and overall survival for post cardiac arrest patients. Hypothermia has also been associated with increasing arrhythomogenic propensity of the heart. In accidental hypothermia cases, marked increases in arrhythmias have been noted (Tiainen et al., 2009). Clinically significant arrhythmias in experimental studies have not been conclusive.

Irreversible brain and heart damage continue to be common outcomes for a post cardiac arrest patient. Therapeutic hypothermia has given patients the best chance of positive cardiac and neurological outcomes. Induced hypothermia has been endorsed by the American Heart Association and the International Liaison Committee on Resuscitation, yet it is absent from many advance cardiac life support protocols in hospitals. This is due to many reasons including the lack of familiarity with the treatment itself, lack of advance protocols, and the limited availability of newer less cumbersome cooling devices (Erb, Hravnak, & Rittenberger, 2012).

Often there is no identifiable cause of arrhythmias associated with hypothermia. For instance, a cardiac arrest patient receiving hypothermia therapy, who also happens to be a trauma victim, could have issues associated with head or chest trauma leading to arrhythmias. Chest traumas specifically lead to contusions of the heart affecting its rhythmicity.

Traumas are common with cardiac arrest patients due to the engaging of activity prior to cardiac arrest. Head traumas such as subarachnoid hemorrhages can lead to arrhythmias. Catecholamines, given as medications after cardiac arrest, can cause heart rhythm disturbances (Bell, 2010). After these factors have been explored, one must take into account the propensity of hypothermia to cause cardiac arrhythmias.

Not all arrhythmias associated with hypothermia are due to reentry. Excessive prolongations of action potentials can lead to early depolarizations, polymorphic ventricular tachycardia, or degenerative ventricular fibrillation (Trohman & Neiger, 2012).

For hypothermic treatment to be effective, cardiac arrest first needs to be recognized quickly, and treatment must be initiated and maintained for 12-24 hours once the desired core temperature has been reached (Tiainen et al, 2009).When initiating hypothermia treatment it is imperative to understand how the treatment works.

It was originally thought that the positive outcomes attributed to therapeutic hypothermia were associated with the lowering of temperature as fast and as low as possible, with patients routinely undergoing severe or deep hypothermia. The benefits of hypothermia treatment were thought to be achieved by decreasing brain metabolism and oxygen demand. Cooling and rewarming temperatures and applications varied greatly until the 1960's when the use of intensive care units became more widely available (Polderman, 2009).

Early History

Hypothermia was considered to offer better outcomes than the standard of care during the 1950's to early 1960's. These positive outcomes were despite uncontrollable cooling methods, variable results, and indeterminate cooling times. By the late 1960's, hypothermia treatment was all but done away with due to substantial problems with patient management. Hypothermia treatment would not come on the radar again until the 1980's after a series of successful animal trials rekindled the interest in hypothermia treatment (Polderman, 2009).

It was postulated that the positive outcomes associated with hypothermia were associated with less drastic changes in temperature. Protective mechanisms were more associated with mild to moderate hypothermia. Patients had drastically fewer adverse reactions and the reactions that

did occur were more manageable (Polderman, 2008). Subsequent studies focused on time, duration, depth, and management of adverse effects.

Recent Advances

Mild therapeutic hypothermia use in the intensive care setting has increased drastically but opportunity still exists for furthering use. Hypothermia use is no longer being restricted to treating only ventricular tachycardia and ventricular fibrillation, but is also used to treat asystole and pulseless electrical activity with success (Lebiedz, 2012). If hypothermia treatment use can be expanded to non-ventricular fibrillation cardiac events, it may be seen as viable option for healthcare providers.

The limited therapeutic options of therapeutic hypothermia are a reason for low levels of adherence to current AHA protocols. Although therapeutic hypothermia has the potential for increased utilization, there are clear contraindications. Some contraindications include pre-existing severe coagulation disorders, relevant head trauma, cardiogenic shock, sepsis, high doses of catecholamines, and significant arrhythmias (Lebiedz, 2012).

The International Liaison Committee on Resuscitation (2002) recommended hypothermia treatment for patients that are unconscious with spontaneous return of circulation. These individuals should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation.

The committee also stated that cooling may be advantageous for other rhythms or in-hospital cardiac arrest. The American Heart Association (2010) added to these guidelines with, "active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C) after resuscitation from cardiac arrest during the first 48 hours after return of spontaneous circulation" (p. 772).

Summary

Originally, therapeutic hypothermia was used with mixed results due to inability to manage adverse effects. There were also issues with the cooling process, with the use ice slabs, or open windows during the winter (Polderman, 2008). Detection and control of arrhythmias were also less reliable due to lack of intensive care units. The units at that time were not equipped to manage cardiac arrest patients being treated with therapeutic hypothermia. Modern intensive care units and anti-arrhythmic medication has increased the viability of therapeutic hypothermia treatment for cardiac arrest patients.

The current literature is inconclusive on clinically significant arrhythmias arising from induced hypothermia. The effects of hypothermia cannot be isolated from other lifesaving measures. Although evidence of arrhythmias remains inconclusive, treatment is endorsed by the American Heart Association and ILCOR to be used in cardiac arrest after return of spontaneous circulation. The neurologic and cardiac protective abilities of hypothermia treatment offer benefits that other treatments cannot.

Results

Of the twelve articles included in this literature review, six are summarized below. They are also summarized in Table 1. These studies include primary research, systemic, and integrative reviews. Univariate analysis, multivariate and heart rate variables were used to determine success based on the initial study. Duration and type of arrhythmia were assessed. This was assessed against normothermic conditions. Any clinically significant differences were noted.

Most of the studies included data on witnessed out of hospital cardiac arrest. Some studies were retrospective studies with duration of days to weeks. Studies included male and female cardiac arrest victims. No gender differences were found. Various outcome scales were used.

Tiainen et al (2009) performed a randomized cardiac arrest trial to determine the effects of hypothermia treatment on arrhythmias in post cardiac arrest patients. To be included patients had to be admitted to the Helsinki University Hospital after resuscitation from an out of hospital cardiac arrest. The cardiac arrest had to be witnessed. Presumed cardiac event had to be ventricular fibrillation or nonperfusing ventricular tachycardia as the initial rhythm. The patient had to be unconscious and 18-75 years of age.

All data were collected Utstein style with the recommended guidelines for uniform reporting of data from out-of-hospial cardiac arrest. Seventy participants were included with no significant differences noted to their baseline characteristics. Cardiac enyzmes were higher in the hypothermia groups. Patients were placed on Holter monitors for which time frame recordings were broken down from 0-24 hours, 24-48, and 14 days.

Arrhythmias were noted as premature ventricular beats (PVB), couplets, ventricular tachycardia, and supraventricular premature beats (SVPB). PVBs and couplets were increased in the hypothermic groups while ventricular tachycardia and ventricular fibrillation did not vary between groups. At 14 days post cardiac arrest, there were no significant differences between the groups. The final outcomes were assessed using the Pittsburgh outcome scale which is a five category scale based on cerebral performance CPC 1-2 indicating favorable outcome. Hypothermia treated patients had a 69% favorable outcome compared to 47% of normothermic treated patients.

Kelly and Nolan (2009) used a systematic search to analyze the effects of hypothermia on the myocardium. Only patients who spoke English and who were older than 18 years of age were used. Excluded were accidental hypothermia, cardiac surgery, traumatic brain injury and fulminant liver failure. These selected studies were assessed and graded using the Scottish Intercollegiate Guidelines Network (SIGN).

Kelly and Nolan (2009) suggested that myocardial function may be improved by mild medically induced hypothermia. This could be due to improved myocardial blood flow, improved microvascular integrity, and reduction in no-flow zones and myocardial necrosis. There was an increase in various arrhythmias including atrial and ventricular arrhythmias and prolonged asystole. These arrhythmias were particularly common at temperatures below 32° C.

Mild hypothermia, which is most closely associated with induced hypothermia treatment, showed no clinically significant increase in arrhythmias. Rather, the study found that cooling was associated with decreased arrhythmias. Positive deflections at the end of the QRS complex called Osborn, or J-waves, were noted on ECG of patients undergoing hypothermia treatment. These usually appear at temperatures of 30° C and below and are also noted to be clinically

insignificant. These waves were attributed to extremely low temperatures in which they appeared and disappeared during rewarming.

T-wave inversion due to prolongation of ventricular repolarization could be seen during mild hypothermia. These were usually associated with myocardial ischemia or repolarization issues of the myocardium.

Poldermann (2008) looked specifically at the mechanism of action that leads to the physiological effects on the myocardium that produces arrhythmias. It was determined that cooling has an effect on electrolytes. A combination of intracellular shift and tubular dysfunction associated with hypothermia can lead to the excretion of electrolytes. These electrolytes primarily associated with this were magnesium, potassium, and phosphate.

The depletion of these electrolytes put the patient at increased risk for arrhythmias. Medically induced hypothermia also caused the prolongation of the duration of action potentials and decreased the rate of spontaneous depolarization therefore making the heart susceptible to arrhythmias, the most common being prolonged intervals between the PR and QT phases and the widening of the QRS complex.

These arrhythmias are uncommon and rarely require further treatment. Overall, mild hypothermia treatment was related to a decreased chance of arrhythmia and also related to a more favorable outcome if defibrillation was needed due to the hypothermia stabilizing the cell membrane. Deep hypothermia was related to unsuccessful defibrillation and unresponsiveness to antiarrhythmic drugs.

Patients in deep hypothermia were most susceptible to atrial fibrillation. Cardioversion at $< 34^{\circ}C$ was frequently unsuccessful leading atrial fibrillation to ventricular fibrillation. The

researchers concluded that, although there is potential for arrhythmias, hypothermia treatment should not be withheld.

Lebiedz et al. (2012) used an observational single-center study in order to analyze electrocardiographic changes, arrhythmias and complication rate before, during and after mild therapeutic hypothermia. One hundred and nine, comatose patients underwent mild therapeutic hypothermia. Excluded from this study were those patients with severe coagulation disorders, sepsis, or poor prognosis.

Most patients met the target temperature of 32-34° C within 6 hours. During this time, a significant decrease in heart rate, and prolongation of PR and QT intervals were noted, but were not thought to be clinically significant. Patients with QT prolongation had not been given medication to lengthen QT intervals nor was it found to be associated with ventricular ectopy or torsades de pointes. No specific gender differences were noted in lengthened QT intervals.

Two patients developed ventricular fibrillation during hypothermia and both had an acute myocardial infarction which the researchers related to acute myocardial ischemia. There were no second or third degree AV-blocks although five patients' treatment ended due to symptomatic sinus-bradycardia.

Storm et al (2011) conducted a 34 patient prospective study to evaluate the incidence of malignant arrhythmias and the possible effects of hypothermia on QT intervals. They followed the guidelines of the American Heart Association and the European Resuscitation Council.

Hypothermia treatment was begun directly after admission. Holter ECG monitor readings were analyzed by two independent experienced observers. Arrhythmias were classified as (3-5) beats, non-sustained beats (between 5 and 29 beats), or sustained ventricular tachycardia (greater than 30 beats).

Three patients experienced ventricular tachyacardia. None experienced torsades de pointes. QT interval was significantly prolonged during hypothermia but decreased after hypothermia to baseline levels. The arrhythmias did not require additional treatment. All patients completed 48 hours of hypothermia treatment without any fatalities.

Mirzoyev et al. (2010) tested the theory that arrhythmogenesis, associated with hypothermia, was due to hypokalemia. An observational retrospective analysis of potassium variability with therapeutic hypothermia was performed along with a correlative analysis of QT intervals and ventricular arrhythmias.

Enrolled were 94 sequential patients that were victims of out-of-hospital cardiac arrest. Their serum potassium levels were monitored meticulously. This study included patients who were victims of ventricular fibrillation and pulseless electrical activity who had return of spontaneous circulation. Seven patients had their treatment discontinued due to advance directives, severe hemodynamic or respiratory failure and family request of withdrawal of care.

Thermoregulation equipment was used to achieve and maintain a core body temperature of 33°C for 24 hours. It was found that serum potassium concentrations dropped considerably during hypothermia. This corresponded with a prolonged QT interval. Polymorphic ventricular tachycardia (PVT) was recurrent in 9 patients, with further treatment of PVT being necessary.

Patients with PVT had a significantly lower potassium level than other patients in their cohorts. QT was analyzed with telemetry recordings within the hour of PVT. When severe hypokalemia was noted anti-arrhythmic and vasoactive drugs had no effects on PVT.

The pro-arrhythmic properties of hypothermia treatment have been well established. It is thereby critical to understand the electrophysiological effects. Piktel et al (2011) tested the hypothesis that stated, “hypothermia-enhanced transmural dispersion of repolarization (DOR) is

a mechanism of arrhthmogenesis in hypothermia" (p. 79). They also investigated the degree of hypothermia, rate of temperature change, and cooling versus warming would have an effect on hypothermia-induced arrhythmia substrates.

Higher heterogeneities of repolarization are correlated with increased reentrant excitation and arrhythmogenesis. The slowing of conduction during introduction of hypothermia reduced arrhythmia susceptibility because it reduces hypothermia-induced repolarization gradients. Hypothermia was shown to increase action potential dispersion and conduction block and reentry occurred where action potential dispersion was greatest. As rewarming occurred, conduction velocity increased but dispersion of repolarization stayed the same increasing the risk of arrhythmias. Interestingly, increases in cooling and rewarming rate did not have an effect on dispersion or repolarization. This suggested that the depth of hypothermia and not the rate had the greatest effect on arrhythmogenesis.

Discussion

The studies explored provided significant insight into medically induced hypothermia and its potential negative effects on cardiac arrhythmias. In addition to some potential adverse reactions to medically induce hypothermia, it has been noted that medically induced hypothermia has a positive effect on cardio and neuro outcomes for patients. It has also been shown that medically induced hypothermia can be managed with success in the intensive care units. Based on these findings it is suggested that induced hypothermia can be used with success in cardiac arrest patients, with the appropriate health care management.

Heart Rate Variability

Medically induced hypothermia patients had greater heart rate variability then normothermic patients. There were two possible explanations. It may be that heart rate variability is inversely proportional to heart rate, and/or that heart rate variability is a response to bradycardia induced by hypothermia.

Second, it may be that there are temperature induced changes in automaticity that increase heart rate variability. The low temperature may hamper atrial synchronization. The heart rate variability induced by hypothermia can have a positive effect on the heart. The cold protects the heart against ischemic events by increasing the perfusion to the cardiac muscle.

Heart rate variability is considered a measure of autonomic influence; therefore disturbances in variability result in increased adverse effects (Mirzoyev et al., 2010). These adverse effects include the increase in ventricular tachycardias. Hypothermia may, in fact, preserve autonomic regulation of the heart. This could be the mechanism by which heart rate variability is preserved. Heart rate variability was associated with more favorable outcomes in

medically induced hypothermia patients. Heart rate variability may, therefore, point to better outcomes for cardiac arrest patients due to it preserving intact autonomic regulation.

Electrocardiographic Changes

In spite of severe prolongation of PR and QT intervals, medically induced hypothermia shows low potential for proarrhythmic life-threatening arrhythmias. There was no clinically significant increase in bradycardia or tachycardia. There was a severe shortening of the QRS interval with subsequent lengthening to QRS interval once hypothermic treatment was ended (Lebiedz, 2012). Most of hypothermia's life-threatening arrhythmias occur when temperatures are below 32°C which is below the recommended therapeutic range. There are significant electrocardiographic changes with induced hypothermia but these changes rarely precipitated life-threatening arrhythmias.

Coagulation concerns

There have been studies that noted the rate of increased bleeding complications with hypothermia treatment. Temperatures below 35°C have been associated with platelet dysfunction (Poldermann, 2009). Clinically significant bleeding has been demonstrated with a trend towards those who had preclinical systemic thrombolysis (Lebiedz, 2012). This may have been cause by sustained cardiocompression or the use of systemic thrombolysis.

Those who underwent percutaneous coronary intervention (PCI) received anticoagulation therapy including combined platelet inhibition and heparin. Coagulation concerns after PCI and hypothermia therapy have mixed results. Observational data supports strict protocols for hypothermia treatment in order to decrease the risk of bleeding.

Observational data indicates that the risk for severe bleeding is low. This could be due to patients with bleeding problems not being able to participate in therapeutic hypothermia

treatment. Those induced hypothermia patients that did have bleeding problems required more red blood cells overall in order to reach desired hemocrit levels (Poldermann, 2009). With that being stated, hypothermia patients fared better after bleeding issues. Bleeding issues could lead to arrhythmias associated with hypotension, but the potential for these issues should be weighed against the overall benefit of hypothermia treatment.

Hypokalemia

Therapeutic hypothermia can lead to a decrease in serum potassium levels. Pro-arrhythmic fluxes in potassium have been seen during the initiation and conclusion of hypothermia treatment (Mirzoyev et al., 2010). During the initiation of therapeutic hypothermia these fluxes have been shown to precipitate PVT's and QT prolongation. This suggests that more rigorous electrolyte testing during induced hypothermia may be required.

When potassium treatment was given, there was no increase in adverse effects. The degree of QT prolongation, whether from hypothermia or hypokalemia was an indicator of increased risk of PVT. Once rewarming was initiated, hypokalemia was less likely to lead to arrhythmias (Mirzoyev et al., 2010). Hypothermia, therefore, seems to beget an arrhythmia susceptibility phase that could potentially be aggravated. Hence hypokalemia can further subvert the cardiac rhythm.

Drug Clearance

Hypothermia significantly slows down the body's metabolic functions. Enzymes have optimum temperatures in which reactions occur. Hypothermia lowers enzymes reactions including the clearance of drugs. This is due to the decreased rate of metabolism in the liver which is highly dependent on enzymes.

Reductions in metabolism have been noted for many intensive care unit drugs. These drugs include propofol, epinephrine, norepinephrine, midazolam, barbituates, opiates, phenytolin, nitrates, and some beta blockers (Poldermann, 2009). Some of these drugs can also have a decreased effect on a patient in hypothermia as is the case with some vasoactive drugs. It is also important to keep in mind volume distribution differences and kidney function in the hypothermic patient.

In general, therapeutic doses should be decreased in order to control toxicity. Another option would be for drugs with longer half-lives to be used when possible. Because of their normal slow metabolism a lower body temperature would affect dosing less (Poldermann, 2009). When increase of dosing is needed it should be done with one time bolus doses instead of increases in maintenance dose (Poldermann, 2009). The controls of dosing and toxicity rates are very important when it comes to controlling arrhythmias. Active drugs in the system could have a synergistic effect when in combination with hypothermia treatment and lead to life threatening arrhythmias.

Therapeutic induced hypothermia has positive outcomes for those affected by cardiac arrest. Lee, et al. (2012) has shown a possible correlation between induced hypothermia and a decrease in myocardial tissue injury. An increased troponin level has been associated with increased mortality in patients without other signs of myocardial necrosis. Patients treated with hypothermia showed a decrease in troponin levels.

It is thought that hypothermia treatment has positive effects on cells ability to make energy. ATP, which is the intracellular energy source for the body, is increased in myocardial cells of those treated with hypothermia. Injured myocardial cells are thought to have metabolic failure (Lee, et al. 2012). An increase in ATP in hypothermia treated cells could be due to more

healthy cells being able to produce energy. This shows injury recovery and ability to make excess energy in the hypothermia treated patients. With energy excess there is less chance for arrhythmia producing potential.

The potential for apoptosis of cells was also decreased under therapeutic hypothermia. The inflammatory response in those who undergo therapeutic hypothermia is decreased. Therefore, self-limiting cellular behavior is also partly inhibited. Expression of genes that signal apoptosis was decreased under hypothermic conditions (Lee, et al.2012). Overall this leads to less cardiac injury and fewer arrhythmias associated with ischemic and damaged myocardial cells.

The paramount issue related to hypothermia benefits seems to be related to timing. Post cardiac arrest benefits are related to early cooling. It is then important for healthcare professionals to recognize those with the potential to benefit from hypothermia treatment.

Limitations

There are multiple limitations in this integrative literature review. There was a plethora of available research on induced hypothermia as a treatment for cardiac arrest. However, there were only a few that dealt with cardiac arrhythmias. Many of the articles available were other literature reviews which pull from the same data sources. This could be due to the recent increased interest in hypothermia treatment. Due to the amount of literature reviews the original interpretation of the primary research could be lost. Therefore, the lack of primary research is a limitation of this review.

The primary research articles that were available included those with limited sample size due to specificity of inclusion. It should also be noted that ethnicity was not specified. Therefore, how these results reflect different ethnicities are not noted. There was no consistency as far as inclusion to the study. These were all convenience samples, and no information was gathered about socioeconomic status, education, or co-morbidities. An increase in sample size and variation is needed.

There was no also no consistency in techniques to determine significant arrhythmias. Due to the different measures of clinical significance the interpretations could be skewed from one article to another. There was also no consistency on inclusion criteria. Criteria should be lessened in order to increase the availability and use of therapeutic hypothermia. The strict criteria could skew the results of hypothermia treatment.

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Recommendations for Nursing

Research

Various research studies about hypothermia and cardiac arrhythmias exist, but there is still a lack of primary research on the subject. Most research currently comes from other integrated reviews. More knowledge is needed with an expanded use of hypothermia treatment. Current research uses the American Heart Association recommendations on hypothermia treatment candidates. There has been suggestion that hypothermia treatment is in fact underused and would benefit from expanding its indications. With expanding the indications it would become more routine and nurses would become more knowledgeable on potential adverse effects of cardiac arrhythmias. In addition to more primary research and expanded use it may be beneficial to research the long term effects of those treated with hypothermia treatment.

Research on hospitals adherence to the International Liaison Committee on Resuscitation would also be beneficial. We now do not know how widespread the adherence is to current recommendations. In knowing who are actually adhereing we can find higher samples for future studies, and potentially make revisions to the current guidelines based on experiences at various hospitals.

Another issue that would be adventatious to look into would be the method of medically induced hypothermia. Different methods may have better results or could be associated with a higher level of cardiac arrhythmias. This could be used to further mitigate hypothermia protocols. It could also help with consistency and quality of care. Determing the easiet and most effective conditions in which to induce hypothermia could further expand its use. Expanded use could help with the limited number of participants in the current studies due to hypothermia suggested protocols limiting qualifying patients.

Education

Intensive care nurses receive additional training to handle critical therapeutic hypothermia patients. This group of nurses are the best equiped to handle hypothermia patients. Healthcare providers need to be cautioned with trying to undertake this treatment in other units besides the intensive care units. Appropriate staff to patient ratios and the appropriate equipment must be available for treating cardiac arrest patients with hypothermia treatment.

Nurses need to be educated on what possible complications can arise from hypothermic treatment. Most important of which is cardiac arrhythmias. Cardiac arrhythmias has the potential to be caused by numerous interventions post cardiac arrest including hypothermia treatment. Nurses should be on observing for QT prolongations that has the ability to potentiate dangerous cardiac arrhythmias. Health care providers should also be taught the importance of monitoring for electrolyte imbalaces, regular blood tests should be taken. Bleeding should also be monitored due to the increase possiblity of hemorrage associated with hypothermia treatment.

There should also be education on the recognition of a patient's suitability for hypothermia treatment. Many patients are candidates but the hypothermic protocols are not instituted. Educating health care professionals about the suitability of patients for hypothermia treatment will offer a better patient outcomes based on current research. There would also be a larger population to base further research on.

APPENDIX A

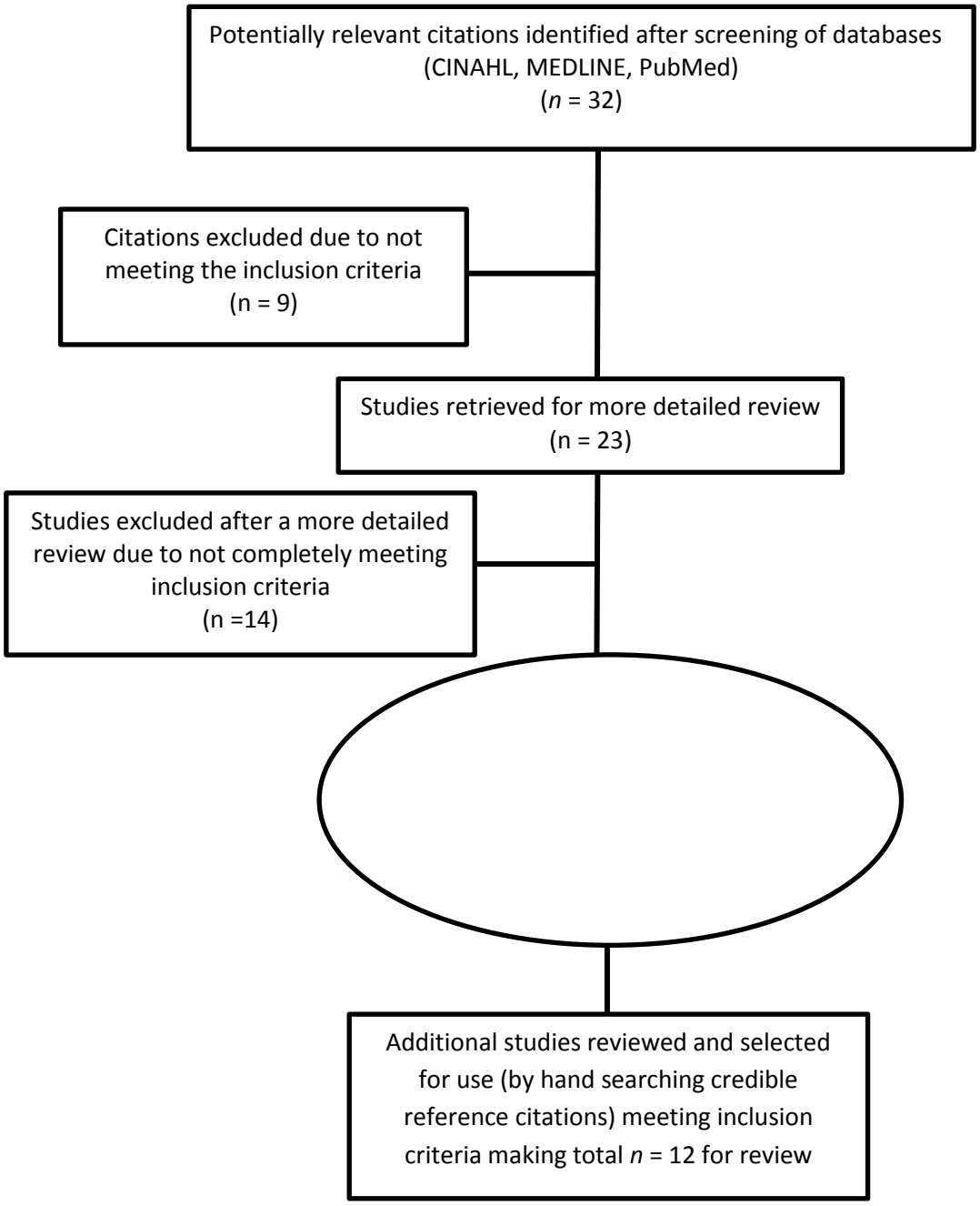
Figures

Figure 1: Consort Diagram

Flow Diagram of Study Selection Process

Key Search Terms = Cardiac Arrest, Induced Hypothermia, Arrhythmias

Limiters = English language, Publication Date of 2003or More Recent



APPENDIX B

Tables

Table 1: Table of Evidence

Article	Kelly, F. E., & Nolan, J. P. (2010). The effects of mild induced hypothermia on the myocardium: A systematic review. *Anaesthesia, 65*(5), 505-515.
Study Design	a systematic review
Purpose	"…pathology of cardiac arrest and myocardial infarction, and the beneficial and harmful effects of mild induced hypothermia." (p. 505)
Participants	58 studies (36 animal studies, 22 human studies)
Results and/or Key Findings	The effects of induced hypothermia on the myocardium remain unknown but studies have stuggested a beneficial effect
Nursing Implications	Patients that are cooled rapidly to achieve target core temperatures for the recommended period of time may improve neurological outcome. "…studies suggest a beneficial effect of induced hypothermia on the heart, but further human studies, possibly in the field of cardiology" (p. 513)
Article	Lebiedz, P., Meiners, J., Samol, A., Wasmer, K., Reinecke, H., Waltenberger, J., & Eckardt, L. (2012). Electrocardiographic changes during therapeutic hypothermia. *Resuscitation, 83*(5), 602-606.
Study Design	observational single-center study without control group
Purpose	To study electrocardiographic changes and associated events of therapeutic hypothermia
Participants	"109 comatose survivors of out-of-hospital cardiac arrest." (602)
Results and/or Key Findings	Treatment lead to a decreased heart rate, significant prolongation of PR and QT intervals and cardiac arrhythmias
Nursing Implications	Induced therapeutic hypothermia can be applied to most patients following out-of-hospital cardiac arrest without increase in risk of arrhythmias notwithstanding noteworthy electrocardiographic changes
Article	Storm, C., Hasper, D., Nee, J., Joerres, A., Schefold, J. C., Kaufmann, J., & Roser, M. (2011). Severe QTc prolongation under mild hypothermia treatment and incidence of arrhythmias after cardiac arrest-A prospective study in 34 survivors with continuous Holter ECG. *Resuscitation, 82*(7),

	859-862
Study Design	prospective single center study
Purpose	"…to evaluate the frequency of malignant arrhythmias and to analyse the possible effects of hypothermia on QTc interval." (859)
Participants	34 out of hospital cardiac arrest patients
Results and/or Key Findings	Significant to severe prolongation was found with no increase in malignant cardiac arrhythmias
Nursing Implications	Close monitoring of QTc interval and healthcare workers should be aware of the potentially malignant arrhythmias arising from QTc prolongation Anti-arrhythmic drugs and antibiotics should be used with caution due to possiblity of further QTc prolongation. "…routine and frequent ECG recording with respect to the QTc interval should become apart of any hypothermia standard operation protocol nd should be recommended by official guidelines" (p.862)
Article	Mirzoyev, S. A., McLeod, C. J., Bunch, T. J., Bell, M. R., & White, R. D. (2010). Hypokalemia during the cooling phase of therapeutic hypothermia and its impact on arrhythmogenesis. *Resuscitation, 81*(12), 1632-1636.
Study Design	Retrospective analysis
Purpose	"…review our experience with the arrhythmogenic milieu during TH and to propose optimal management strategies."(1632)
Participants	94 sequential out of hospital cardiac arrest patients
Results and/or Key Findings	Therapeutic hypothermia is associated with significant decline in potassium during cooling. Hypothermic core temperatures do not protect against arrhythmias and potassium supplementation is suggested
Nursing Implications	Induced therapeutic hypothermia during the cooling phase is especially associated with decreases in serum potassium. Serum potassium should be monitored to not go below 3.0 to avoid arrhythmias Decrease in potassium is associated with the propensity for the develoment of PVT.

Article	Tiainen, M., Parikka, H. J., Mäkijärvi, M. A., Takkunen, O. S., Sarna, S. J., & Roine, R. O. (2009). Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest. *Critical Care Medicine*, *37*(2), 403-409.
Study Design	A prospective comparative substudy of a randomize controlled trial of out of hosptial cardiac arrest patients undergoing therapeutic hypothermia
Purpose	To evaluate post cardiac arrest hypothermia effects on arrhythmias and heart rate variability
Participants	70 consecutive adults patients resuscitated after out of hospital ventricular fibrillation
Results and/or Key Findings	Preserved heart rate variability 24-48 hours may be a predictor of favorable outcomes for cardiac arrest patients treated with therapeutic hypothermia
Nursing Implications	Therapeutic hypothermia was not associated with increased arrhythmias but there were vast electrocardiographic changes. Heart rate variability should be monitored due to its association with positive cardiac outcomes.
Article	Polderman, K. H. (2008). Induced hypothermia and fever control for prevention and treatment of neurological injuries. *The Lancet*, *371*, 1955-69
Study Design	A systematic review
Purpose	"…to provide information to help guide treatments more effectively with regard to timing, depth, duration, and effective management of side-effects." (1955)
Participants	77 patients in whom cooling was initiated very early during transportation in an ambulance to the hospital after cardiopulmonary resuscitation, 273 patients witnessed cardiac arrests
Results and/or Key Findings	Hypothermia has highly promising benefits but remains widely underused especially in the USA
Nursing Implications	Hypothermia treatment is drastically underused in the US. "Studies that establish optimum depth and duration of cooling are also needed" (p. 1965).

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