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SAVREMENI ASPEKTI UPRAVLJANJA POVIŠENOM TELESNOM TEMPERATUROM

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SAŽETAK

Cilj ovog preglednog rada je bio da se na sistematičan način prikažu savremeni načini upravljanja telesnom temperaturom. Povišena telesna temperatura, jedna je od najstarijih, najpoznatijih i najbolje uočenih manifestacija bolesti. Ona je normalan, koordinisan odgovor organizma na identifikovanu pretnju imunološkom sistemu, što uključuje autonomni, bihejvioralni i neuroendokrini odgovor. Upravljanje povišenom telesnom temperaturom sastavni je aspekt zdravstvene nege na svim nivoima zdravstvene zaštite. Postoje dva osnovna pristupa u rešavanju ovog problema: farmakološko i fizičko zbrinjavanje. U okviru fizičkih metoda zbrinjavanja dostupne su nekontrolisane konvencionalne metode, intravaskularne i perkutane kontrolisane metode, a od farmakoloških, najčešće se primenjuju antipiretici.

Ključne reči: groznica, telesna temperatura, menadžment

Uvod

Povišena telesna temperatura (TT), jedna je od najstarijih, najpoznatijih i najbolje uočenih manifestacija bolesti. Povišena telesna temperatura je normalan, koordinisan odgovor organizma na identifikovanu pretnju imunološkom sistemu, što uključuje autonomni, bihejvioralni i neuroendokrini odgovor (1). Takođe, kao odgovor organizma na stimulus, povišena TT se može javiti kao reakcija na endogene provokacije, te tada ima za cilj da potpomogne imunološkom sistemu. Normalnu vrednost TT održava termoregulacioni centar i to između 36,1^{o}C i 37,5^{o}C. Kod većine pacijenata, povišena TT je korisna i ne zahteva ozbiljnu medicinsku intervenciju, ali veoma često se dešava da od povišene TT pacijent nema očekivanu korist, već je značajno povezana sa lošim ishodom (2) i zahteva strategiju za snižavanje (3). Povišena TT je česta kod hospitalizovanih pacijenata i procenjuje se da se javlja kod gotovo polovine pacijenata tokom perioperativne nege (4). Do povišene TT mogu dovesti brojni faktori, poput različitih infekcija, zapaljenja, reakcije na lekove, neoplazme, autoimune bolesti, kao i vaskularne okluzivne bolesti (5). U većini slučajeva, povišena TT nastaje stvaranjem endogenih pirogena iz mononuklearnih i polimorfonuklearnih leukocita. Najmoćniji od endogenih pirogena su interleukin-1, interleukin-6 i faktor nekroze tumora α (alfa), koji stimulišu proizvodnju metabolita arahidonske kiseline (prostaglandin E-2 i tromboksan A-2), koji deluju na centralni nervni sistem, odnosno na područja koja utiču na regulaciju TT u hipotalamusu i produženoj moždini (6). Tačan mehanizam kojim cirkulišući citokini u sistemskoj cirkulaciji utiču na nervno tkivo ostaje delimično nejasan. Složenost febrilnog odgovora može se pripisati njegovim sistemskim efektima diktiranim endokrinim, neurološkim i imunološkim mehanizmima ponašanja (6). Fiziološki odgovor organizma na povišenu TT uključuje niz kardiovaskularnih i metaboličkih promena poput povećane potrošnje kiseonika, povećanog minutnog srčanog volumena i intenzivnije proizvodnje kateholamina u serumu.

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MODERN ASPECTS OF FEVER MANAGEMENT

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SUMMARY

The aim of this review article was to present in a systematic way modern aspects of body temperature management. A fever is one of the oldest, best known and best observed manifestations of the disease. It is a normal, coordinated body's response to an identified threat to the immune system, including the autonomic, behavioral and neuroendocrine response. Fever management is an integral aspect of health care at all levels of health care. There are two basic approaches to solving this problem: pharmacological and physical care. Uncontrolled conventional methods, intravascular and percutaneous controlled methods are available within physical methods of care, while pharmacological methods most frequently include the use of antipyretics.

Key words: fever, body temperature, management

Introduction

A fever is one of the oldest, best known and best observed manifestations of disease. It is a normal, coordinated body's response to an identified threat to the immune system, including the automatic, behavioral and neuroendocrine response (1). In addition, as the body's response to a stimulus, a fever may occur as a reaction to endogenous provocations, and then it aims to support the immune system. The normal value of body temperature is maintained by the thermoregulatory center and it ranges between 36.1°C and 37.5°C. In most patients, a fever is beneficial and it does not demand serious medical intervention, however, it happens very often that the patient does not benefit from the fever, and it is significantly associated with a poor outcome and requires a strategy to lower it (2). Hyperthermia is common in hospitalized patients and it is estimated that it occurs in almost half of patients during the perioperative care (4). Numerous factors can lead to hyperthermia, such as: various infections, inflammation, reactions to drugs, neoplasmas, autoimmune diseases, as well as occlusive arterial diseases (5). In most cases, hyperthermia is caused by the creation of endogenous pyrogens from mononuclear and polymorphonuclear leukocytes. The most powerful endogenous pyrogens are interleukin-1, interleukon-6 and tumor necrosis factor α (alpha), which stimulate the production of metabolites of arachidonic acid (prostaglandin E-2 and thromboxane A-2), which affect the central nervous system, that is, the areas that influence the regulation of body temperature in the hypothalamus and medulla oblongata (6). The exact mechanism, by which the circulating cytokines affect the neural tissue in the systemic circulation, remains partially unknown. The complexity of the febrile response may be attributed to its systemic effects which are dictated by endocrine, neurological and immune mechanisms of behavior (6). The body's physiological response to a rise in body temperature includes a series of cardiovascular and metabolic changes including increased oxygen consumption, increased cardiac output and more savremenim aspektima menadžmenta (upravljanja) povišenom telesnom temperaturom.

Metode

U okviru ovog preglednog rada uključene su sve studije do kojih se došlo na osnovu pretraživanja sledećih baza podataka: PubMed, CINAHL, PubMed, Web of Science i Embase. U svrhu pretraživanja korišćene su tri ključne reči: groznica, telesna temperatura i menadžment. U analizi podataka korišćeni su rezultati samo onih studija koje su objavljene na engleskom jeziku u periodu od januara 2000. do juna 2023. godine.

Mehanizam termoregulacije

Hipotalamus je glavni prekidač koji radi kao termostat za regulisanje telesne temperature. Ako je TT previsoka, hipotalamus može pokrenuti nekoliko procesa kako bi je snizio. Ovo uključuje povećanje cirkulacije krvi na površini tela kako bi se omogućilo rasipanje toplote kroz kožu i početak znojenja kako bi se omogućilo isparavanje vode na koži da bi se površina ohladila (7). Mehanizam termoregulacije podrazumeva: znojenje, drhtavicu, vazodilataciju i vazokonstrikciju. Znojenje povećava gubitak telesne toplote povećanjem isparavanja znoja. Drhtanje proizvodi toplotu nehotičnim kretanjem mišića. Vazodilatacija i vazokonstrikcija se odnose na promene u krvnim sudovima, koji utiču na temperaturu kože promenom brzine cirkulacije krvi (8). Naime, hipotalamus prvenstveno deluje kao kontrolor gubitka toplote u telu, te svaki porast temperature iznad zadate tačke registruje i dalje šalje nervne impulse za aktiviranje vazodilatacije i znojenja, odnosno aktivira mehanizme gubitka toplote u telu. Pomenuti mehanizam je toliko precizan da se razlike u TT pri vazodilataciji i znojenju razlikuju za svega deseti deo stepena u odnosu na TT pri vazokonstrikciji i iznose nešto više od 37ºC. Isti mehanizam reguliše i vrednost TT pri drhtanju koja je nešto niža od 36ºC. (9). Takođe, temperatura kože ima sporednu ulogu u kontroli hlađenja tela.

Pri istoj temperaturi unutar centralnog termoregulacionog sistema (CTS), viša temperatura kože može povećati brzinu znojenja, a hladnija je inhibira (8). Svaki termoregulacioni odgovor ima svoj prag, nakon koga dolazi do aktiviranja regulacije temperature na nivou CTS. Prekapilarna vazodilatacija i znojenje su sinhroni procesi i imaju isti prag temperature unutar CTS. Temperature između pragova znojenja i sužavanja krvnih sudova definišu normalnu vrednost telesne temperature – obično oko 37°C (9). Temperature CTS su obično veće kod žena nego kod muškaraca i variraju za oko 1°C na cirkadijalnoj osnovi (8). Hipotalamički regulatorni mehanizmi za regulaciju TT mogu dovesti do pojave povišene TT (febrilnosti) u odgovoru na sindrom sistemskog inflamatornog odgovora. Ovaj sindrom je obično iniciran prisustvom citokina (interleukin (IL)-1β, IL-6 i faktor nekroze tumora (TNF)). On može biti posledica delovanja različitih infektivnih agenasa, uključujući bakterijske, virusne i parazitske infekcije, ali i različitih faktora neinfektivne prirode, kao što su ozbiljan pankreatitis i obimne hirurške intervencije.

Faktori koji utiču na promenu telesne temperature

Veliki je broj faktora koji na posredan ili neposredan način mogu uticati na dnevnu fluktuaciju TT. Naime, naučno dokazane činjenice koje treba uzeti u obzir prilikom merenja TT, a koje idu u prilog promeni vrednosti od ±0,5ºC su: pol, starost i mesto merenja (10). Izloženost različitim medikamentima, posebno anesteticima, analgeticima i generalno imunosupresivnoj terapiji, kao i u akutnoj etiologiji neinfektivnih i zaraznih bolesti u perioperativnim i intenzivnim uslovima lečenja, mogu se javiti abnormalnosti koje utiču na porast TT u odnosu na normalne vrednosti (6). Rezultati nedavno objavljenih kliničkih ispitivanja ukazuju na to da se agresivne promene TT najčešće mogu sresti kod postreanimacionih stanja, odnosno kod pacijenata koji su u postreanimacionoj komi u oporavku od reanimacije. Takođe, povišena TT može da bude odbrambeni odgovor organizma na delovanje pirogenih agenasa koji se oslobađaju kao deo zapaljenskog procesa, uzrokujući pojačan imunološki odgovor i zaštitu organizma od uzročnika infekcija (6). Zbog visokog rizika od infekcije povezane sa invazivnim procedurama, imunosupresijom, patološkim stanjima i drugim rizicima povezanim sa hospitalizacijom u jedinici intenzivnog lečenja (JIL), febrilnost se javlja kod više od jedne trećine kritično obolelih pacijenata (8). Zbog toga je čest događaj da u JIL više od 50% hospitalizovanih pacijenata ima povišenu TT uzrokovanu infektivnim ili neinfektivnim agensima (11). Uzroci povišene TT kod pacijenata u JIL su često sledeće bolesti: pneumonija povezana sa mehaničkom ventilacijom, infekcija krvotoka povezana sa cenintensive production of catecholamines in the serum.

The aim of this review article is to present in a systematic way the results of previous research on modern aspects of fever management.

Methods

This review article includes all studies that were found during the search of the following databases: PubMed, CINAHL, Veb of Science and Embase. Three keywords were used for the search: fever, body temperature and management. The results of those studies that were published in English from January 2000 to June 2023 were used for the analysis of data.

The mechanism of thermoregulation

The hypothalamus is the main switch that works like a thermostat for the regulation of body temperature. If body temperature is too high, the hypothalamus can initiate several processes in order to lower it. This includes an increase in blood circulation on the surface of the body in order to allow heat to dissipate through the skin and the initiation of sweating in order to allow the evaporation of water on the skin to cool the surface (7). The mechanism of thermoregulation includes: sweating, shivering, vasodilatation and vasoconstriction. Sweating increases the loss of body heat by increasing the evaporation of sweat. Shivering produces heat through involuntary muscle movements. Vasodilatation and vasoconstriction refer to changes in blood vessels, which affect the skin temperature by changing the speed of blood circulation (8). Namely, the hypothalamus primarily acts as a controller of heat loss in the body, and it registers every rise in temperature above the set point and further sends nerve impulses for the activation of vasodilatation and sweating, that is, it activates the mechanisms of heat loss in the body. The above mentioned mechanism is so precise that differences in body temperature during vasodilatation and sweating differ by only one tenth of a degree in comparison to body temperature during vasoconstriction and they amount to slightly more than 37^{o}C. The same mechanism regulates the value of body temperature when shivering, which is slightly lower than 36^{o}C (9). Also, the skin temperature has a secondary role in controlling the body cooling.

At the same temperature within the central thermoregulatory system (CTS), a higher skin temperature can increase the speed of sweating, whereas it is inhibited by a lower temperature (8). Each thermoregulatory response has its own threshold, after which the regulation of temperature is activated at the level of CTS. Precapillary vasodilatation and sweating are synchronous processes that have the same temperature threshold within the CTS. Temperatures between the thresholds of sweating and constriction of blood vessels define the normal value of body temperature – usually around 37^{o}C (9). CTS temperatures are usually higher in women than in men and they vary by about 1^{o}C on a circadian basis (8). The hypothalamic regulatory mechanisms for the regulation of body temperature cam lead to the appearance of high temperature (febrility) in response to the systemic inflammatory response syndrome. This syndrome is usually initiated by the presence of cytokines (interleukin (IL)-1ß, IL-6 and tumor necrosis factor (TNF)). It can be the consequence of different infectious agents, including bacterial, viral and parasitic infections, but also of different non-infectious agents, such as severe pancreatitis and extensive surgical interventions.

Factors that affect the change in body temperature

There are a lot of factors that can influence the daily fluctuation of body temperature in a direct or indirect way. Namely, the scientifically proven facts that should be taken into account when measuring body temperature, and which are in favor of a change in value of +0.5^{o}C, are the following: sex, age, place of measurement (10). Exposure to various medications, especially anesthetics, analgesics and generally to immunosuppressive therapy, as well as in the acute etiology of non-infectious and infectious diseases in perioperative and intensive treatment conditions, abnormalities that affect the rise in body temperature in comparison to normal values may appear (6). The results of recently published clinical studies indicate that aggressive changes in body temperature may be encountered most often in post-resuscitation conditions, that is, in patients who are in post-resuscitation coma recovering from reanimation. Also, a fever may be a defensive response of the body to the action tralnim venskim kateterom, infekcija urinarnog trakta povezana sa urinarnim kateterom, pseudomembranozni kolitis povezan sa bakterijom *Clostridium difficile*, perforirajući stres ulkus i infekcija povezana sa hirurškom ranom (11).

Neinfektivni poremećaji koji mogu dovesti do povišene TT kod pacijenata hospitalizovanih u JIL su: postoperativna groznica, posttransfuzijske groznice, groznice izazvane primenom određenih lekova, infarkt mozga ili srca, cerebelarna krvarenja, bubrežna insuficijencija, pankreatitis, aspiracioni pneumonitis, akutni respiratorni distres sindrom (ARDS), duboke venske tromboze, plućna embolija i dekubitalni ulkus (12).

Monitoring telesne temperature

TT je jedan od četiri glavna vitalna parametra. Iako je merenje TT deo rutinske kliničke prakse, postoje velike varijacije u metodama i tehnikama merenja telesne temperature. Precizno merenje TT, kao i efikasno i kontinuirano nadgledanje temperaturne fluktuacije omogućavaju da se pojedina stanja uoče na vreme, što dalje omogućava pravovremeno reagovanje i sprovođene određenih intervencija i procedura. Prilikom merenja TT neophodno je koristiti najprikladniju tehniku kako bi bili sigurni da se temperatura tačno meri. Netačni rezultati mogu uticati na dijagnozu i lečenje, dovesti do neuspeha u identifikovanju pogoršanja stanja pacijenta i ugroziti bezbednost pacijenata. Tačnost procene vrednosti TT zavisi od nekoliko faktora, poput metode merenja, mesta (lokalizacije) merenja, pouzdanosti uređaja pomoću kog se vrši merenje, kao i obučenosti zdravstvenog radnika (10). Ne postoji jedinstvena TT, već temperatura tkiva uveliko varira od mesta do mesta, te se tako vrednosti merenja razlikuju uglavnom u odnosu na perfuziju tkiva.

Tehnike merenja TT su različite, te bi njihova osnovna podela bila na invazivne i neinvanzivne tehnike merenja. Svakako, invanzivne tehnike merenja, poput postavljanja temperaturne sonde u jednjak, plućnu arteriju ili mokraćnu bešiku, daju najpouzdanije vrednosti merenja TT, ali su takve tehnike merenja ipak namenjene kritično obolelim pacijentima, jer zahtevaju posebne uslove za izvođenje procedure. Konvencionalno, neinvanzivno merenje TT podrazumeva merenje na dostupnijim mestima: ispod jezika, u aksilama, rektumu i spoljašnjem ušnom kanalu. Neinvanzivne tehnike merenja TT ne zahtevaju posebne uslove za izvršenje procedure, te su takvi načini merenja najpristupačniji na svim nivoima zdravstvene zaštite. Kada je reč o neinvanzivnom merenju TT važno je održati doslednost u odabiru mesta merenja, radi mogućnosti poređenja vrednosti, imajući u vidu da postoje izvesne razlike u vrednostima na različitim mernim mestima. Da bi se postigla preciznija termometrija, veoma je važno uzeti u obzir sve faktore koji utiču na merenje telesne temperature uključujući tehničke karakteristike, konfiguraciju uređaja, kalibraciju, održavanje i preporuke za korišćenje date od strane proizvođača.

Terapeutska hipotermija

Ciljano upravljanje TT (eng. *Targeted temperature management* - TTM), ranije poznato kao blaga terapijska hipotermija, kod pacijenata koji su preživeli vanbolnički iznenadni srčani zastoj može značajno poboljšati stope dugotrajnog neurološkog oštećenja, a moglo bi se pokazati kao jedan od najvažnijih kliničkih napredaka u resuscitacionoj nauci (11). Ciljano upravljanje temperaturom putem indukovane hipotermije (između 32−36°C) trenutno se smatra tretmanom prve linije tokom lečenja pacijenata nakon srčanog zastoja koji su primljeni na odeljenje intenzivnog lečenja. Naime, svaki deseti pacijent ima srčani zastoj, a od njih samo polovina preživi u prihvatljivom neurološkom stanju. Pacijenti koji su preživeli srčani zastoj imaju postreanimacioni sindrom kog karakterišu oštećenje mozga, disfunkcija miokarda, sistemski ishemijsko-reperfuzijski sindrom, kao i kliničke komplikacije nastale kao posledica srčanog zastoja (10). Cilj TTM-a je omogućiti neuroprotekciju i smanjiti sekundarna neurološka oštećenja uzrokovana anoksijom. Hipotermija nudi različite potencijalno korisne efekte u upravljanju postreanimacionim sindromom: smanjuje metaboličku aktivnost dozvoljavajući na taj način organima da tolerišu duže periode ishemije bez nepopravljivih oštećenja, i u stanju je da smanji štetne efekte reperfuzije, posebno neurološka oštećenja izazvana oslobađanjem inflamatornih medijatora nakon obnavljanja krvotoka. Zauzvrat, hipotermija takođe smanjuje inflamatorni odgovor i porast intrakranijalnog pritiska, kao i rizik od sekundarne groznice zbog sistemske inflamatorne reakcije. U ovom sindromu postoji kritično vremensko razdoblje koje pokriva period između oporavka spontane cirkulacije i of pyrogenic agents that are released as part of the inflammatory process, causing an increased immune response and protection of the body against infectious agents (6). Due to the high risk of infection associated with the invasive procedures, immunosuprression, pathological conditions and other risks related to hospitalization in intensive care units (ICUs), febrility occurs in more than one-third of critically ill patients (8). Therefore, it is common that more than 50% of patients who are hospitalized in ICUs have a fever caused by infectious or non-infectious agents (11). The causes of fever in ICU patients are often the following diseases: pneumonia associated with mechanical ventilation, bloodstream infection associated with a central venous catheter, urinary tract infection associated with a urinary catheter, pseudomembranous colitis associated with the bacterium Clostridium difficile, perforating stress ulcus and infections associated with surgical wounds (11).

Non-infectious disorders that can lead to fever in patients hospitalized in ICUs are the following: postoperative fever, post-transfusion fever, fever caused by certain drugs, brain or heart infarction, cerebral hemorrhage, renal insufficiency, pancreatitis, aspiration pneumonitis, acute respiratory distress syndrome (ARDS), deep vein thrombosis, pulmonary embolism and pressure ulcers (12).

Body temperature monitoring

Body temperature (BT) is one of the four main vital parameters. Although measuring BT is part of routine clinical practice, there are great variations with regard to the methods and techniques for measuring body temperature. Precise measuring of BT, as well as effective and continuous monitoring of body fluctuations allow certain conditions to be detected in time, which further enables timely response and implementation of certain interventions and procedures. When measuring BT, it is necessary to use the most appropriate technique in order to ensure accurate measuring. Inaccurate results may affect the diagnosis and treatment, lead to failure regarding the identification of deterioration of patient's state and endanger the patient's safety. The accuracy of the assessment of values of BT depends on several factors, such as the method of measurement, place (localization) of measurement, the reliability of the device that is used for the measurement, as well as health care worker's skills (10). There is no single body temperature, however, the tissue temperature significantly varies from place to place, so the measurement values differ mainly in relation to tissue perfusion.

Measurement techniques are different, and therefore, the basic classification includes invasive and non-invasive measurement techniques. Certainly, invasive measurement techniques , such as placing a temperature probe in the esophagus, pulmonary artery or bladder, give the most reliable measurement values, but such measurement techniques are intended for critically-ill patients, because they require special conditions for performing the procedure. Conventional, non-invasive measurement of BT involves the measurement in places that can be easily accessed: under the tongue, in the axilla, rectum and external auditory canal. Non-invasive techniques of measurement of BT do not require special conditions for performing the procedure, and therefore, such measurement methods are the most accessible at all levels of health care. As far as non-invasive measurement of body temperature is concerned, it is important to maintain the consistency in the selection of the measurement site, so that values could be compared, having in mind differences in values when body temperature is measured at different sites. In order to achieve more precise thermometry, it is very important to take into consideration all the factors that influence body temperature measurement including technical characteristics, device configuration, calibration, maintenance and recommendations for usage provided by the manufacturer.

Therapeutic hypothermia

Targeted temperature management (TTM), which was formerly known as mild therapeutic hypothermia, in patients who have survived after the out-of-hospital sudden cardiac arrest, can significantly improve the rates of long-term neurological damage, and it may prove to be one of the most important clinical advances in the science of resuscitation (11). Targeted temperature management with the help of induced hypothermia (between 32-36^{o}C) is currently considered to be the first-line treatment during the treatment of patients who suffered pokretanja upalnog odgovora, u kojem smanjenje TT može imati blagotvorne efekte. Veruje se da ovaj period može trajati oko 4–5 sati (11).

Metode perifernog hlađenja

U kliničkoj praksi postoje različite metode za indukovanje, održavanje i vraćanje TT u fiziološke okvire. Dostupne su nekontrolisane konvencionalne metode, intravaskularne i perkutane kontrolisane metode. Optimalni način hlađenja podrazumeva neophodan multimodalni pristup za rešavanje sve tri faze hlađenja: indukciju, održavanje i ponovno zagrevanje. Generalno, najveći broj studija sugeriše na korišćenje dve kombinovane metode indukovane hipotermije: površinsko hlađenje i endovaskularno hlađenje(13-15).

Površinske metode hlađenja uključuju primenu posebno dizajniranih ploča za hlađenje, koje omogućavaju smanjenje TT za 3,5°C/sat i koje se najčešće koriste u savremenoj kliničkoj praksi. Tehnika površinskog hlađenja pomoću hipokarbonskih ploča za hlađenje je jednostavna i brza za izvođenje, čak i u vanbolničkim uslovima. Ipak, u kliničkoj praksi se još uvek mogu sresti i konvencionalne metode hlađenja, poput vazdušnih dušeka, ledenih obloga i alkoholnih frikcija. Prednost površinskog hlađenja je u tome što ne zahteva naprednu opremu ili stručnost u postavljanju intravaskularnog katetera i izbegava rizike povezane sa postavljanjem centralnog venskog katetera. U studijama koje se bave procenom savremenih sistema za hlađenje apsolutna prednost se daje savremenim sistemima za hlađenje poput pomenutog koji snižava TT za 3,5°C/sat i neinvanzivan je u odnosu na invanzivne metode rashlađivanja čija je maksimalna brzina rashlađivanja 2°C/sat (15).

Endovaskularno hlađenje pomoću katetera je invanzivna procedura, koja zahteva kraće vreme za postizanje ciljne temperature u odnosu na konvencionalne metode hlađenja (16). Kod primene endovaskularnog hlađenja pacijenata, važna odrednica efikasnog hlađenja je površina tela. Ipak, plasiranje endovaskularnog katetera zahteva dostupnst opreme i uslova, kao i postojanje kontrolne rashladne jedinice koja sadrži integrisane rashladne sisteme i mogućnost strože i preciznije kontrole TT kako bi se uspešno izbeglo prekoračenje i slučajno zagrevanje pacijenta, te nenamerno povećanje intrakranijalnog pritiska i cerebralni edem. Takođe, kod upotrebe ovog načina hlađenja, neophodno je smanjiti drhtavicu pacijenta radi efikasnije razmene toplote. Neželjeni događaji povezani sa endovaskularnim hlađenjem uključuju upalu pluća, srčanu aritmiju, trombocitopeniju i vaskularnu disekciju (16).

Bez obzira o kojoj metodi hlađenja se radi, zaštitni mehanizmi protiv hipotermije uključuju drhtavicu mišića i kožnu vazokonstrikciju. Vazokonstrikcija kože smanjuje provodljivost toplote kroz kožu, dok drhtanje proizvodi energiju i toplotu kroz ponavljajuće kontrakcije mišića. Pored supstanci koje menjaju kontrolu temperature hipotalamusa, neuromuskularni blokatori su efikasni protiv drhtavice. U kliničkim ispitivanjima hipotermije kod pacijenata nakon srčanog zastoja, neuromuskularna blokada je najčešće korišćena za sprečavanje i lečenje drhtavice. Drhtanje kod svesnog pacijenta stvara nelagodu i smanjuje efikasnost hlađenja. Većina pacijenata sa velikim ishemijskim moždanim udarom ima smanjeno stanje svesti, te da bi se osigurala udobnost pacijenta i efikasno rashlađivanje, drhtavica se mora smanjiti centralno aktivnim sredstvima. Kod pacijenata koji primaju endovaskularnu hipotermiju, površinski pokrivači za zagrevanje kože mogu smanjiti prag drhtavice i povećati toleranciju i udobnost pacijenata. Većina podataka o kontroli drhtavice dolazi iz istraživanja za kontrolu drhtavice nakon anestezije (10).

Primena antipiretika

Pored prethodno opisanog fizičkog hlađenja, u terapiji febrilnih pacijenata mogu se koristiti i antipiretici. Antipiretik može smanjiti telesnu temperaturu smanjenjem praga kontrole telesne temperature u hipotalamusu. Postoje dve kritične pretpostavke kod primene antipiretičke terapije. Jedna pretpostavka je da je povišena TT bar delimično štetna, a druga pretpostavka je da će suzbijanje febrilnosti smanjiti, ako ne i eliminisati, štetne efekte povišene TT. Nijedna od navedenih pretpostavki nije eksperimentalno potvrđena, ali kako je povišena TT uobičajeni znak infekcije, tako se smatra jasnim signalom inflamacije. Febrilni odgovor kao komponenta procesa febrilnosti podrazumeva kompleksnu reakciju organizma na patogene što uključuje rast TT posredovane delovanjem citokina i aktiviranjem brojnih fizioloških, endokrinoloških i imunoloških mehanizama.

Antipiretici podrazumevaju grupu lekova koji inhibiraju proizvodnju prostaglandina, a nastaju delovanjem enzima ciklooksigenaza (COX). Inhibicija COX-1 uzrokuje štetne nuspojave, a inhibicija from cardiac arrest and who were admitted to the intensive care unit. Namely, every tenth patient has cardiac arrest, while only half of them survive and have acceptable neurological condition. Patients who survived cardiac arrest have a post-resuscitation syndrome, which is characterized by brain damage, myocardial dysfunction, systemic ischemia-reperfusion syndrome, as well as clinical complications resulting from cardiac arrest (10). The goal of TTM is to enable the neuroprotection and reduce secondary neurological damage caused by anoxia. Hypothermia offers different, potentially beneficial effects in the management of post-resuscitation syndrome: it reduces the metabolic activity, thus allowing organs to tolerate longer periods of ischemia without irreparable damage, and it is able to reduce the harmful effects of reperfusion – especially neurological damage caused by the release of inflammatory mediators after the reperfusion. In turn, hypothermia also reduces the inflammatory response and increase in intracranial pressure, as well as the risk of secondary fever due to a systemic inflammatory reaction. In this syndrome, there is a critical time period covering the period between the recovery of spontaneous circulation and the initiation of inflammatory response, in which a decrease in body temperature can have beneficial effects. It is believed that this period can last around 4-5 hours (11).

Methods of peripheral cooling

In clinical practice, there are various methods for inducing, maintaining and returning body temperature to physiological limits. Uncontrolled conventional methods, intravascular and percutaneous controlled methods are available. The optimal method of cooling implies the necessary multimodal approach used for solving all three phases of cooling: induction, maintenance and reheating. Generally speaking, the majority of studies suggest the use of two combined methods of induced hypothermia: surface cooling and endovascular cooling (13-15).

Surface cooling methods include the application of specially designed cooling plates, which enable the decrease in BT by 3.5°C per hour and which are most often used in modern clinical practice. The technique of surface cooling with the help of hypocarbon plates is simple and can be quickly performed, even in outpatient conditions. However, conventional cooling methods such as air mattresses, ice packs and alcohol frictions can still be seen in clinical practice. The advantage of surface cooling is that it does not require advanced equipment or expertise to place the intravascular catheter and it avoids the risks connected with the placement of central venous catheter. In studies, which assess the contemporary cooling systems, the absolute advantage is given to modern cooling systems, such as the above mentioned system, which lowers BT by 3.5°C per hour and it is non-invasive in comparison to invasive cooling methods, whose maximum cooling rate is 2°C/hour (15).

Endovascular cooling using a catheter is an invasive procedure, which demands a shorter time necessary to reach the target temperature in comparison to conventional cooling methods (16). When endovascular cooling of patients is applied, an important determinant of efficient cooling is the body surface area. However, placing the endovascular catheter requires the availability of equipment and conditions, as well as the existence of a control cooling unit, which contains integrated cooling systems and the possibility of stricter and more precise control of body temperature in order to successfully avoid the overshoot and accidental warming of the patient, and the inadvertent increase in intracranial pressure and cerebral edema. Also, when this cooling method is used, it is necessary to reduce the patient’s shivering for the more efficient heat exchange. Adverse events related to endovascular cooling include pneumonia, cardiac arrhythmia, thrombocytopenia, and vascular dissection (16).

Regardless of which cooling method is used, protective mechanisms against hypothermia include muscle shivering and cutaneous vasoconstriction. Cutaneous vasoconstriction reduces thermal conduction through skin, while shivering produces energy and heat through repetitive muscle contractions. In addition to the substances that change the hypothalamic temperature control, neuromuscular blocking agents are efficient against shivering. In clinical trials of hypothermia in patients after cardiac arrest, neuromuscular blockade is most commonly used to prevent and treat shivering. Shivering in a conscious patient causes discomfort and reduces the efficiency of cooling. The majority of patients with major ischemic stroke have a lowered level of

COX-2 smanjuje upalu, temperaturu i bol (15). Antipiretici koji se najčešće upotrebljavaju u kliničkoj praksi za lečenje povišene TT su paracetamol, ibuprofen i diklofenak, te u određenim indikacijama naproksen. Razlozi za upotrebu antipiretičke terapije uključuju ublažavanje tegoba, smanjenje morbiditeta i mortaliteta, prevenciju febrilnih napada, smanjenje kognitivnih oštećenja, kao i smanjenje komplikacija moždanog udara ili povreda mozga. Primena antipiretičkih lekova posebno je značajna za sedirane pacijente. Sedacija bi trebalo da potisne hladne reakcije, pa bi sedacija u kombinaciji sa fizičkim hlađenjem trebalo da bude efikasna za smanjenje telesne temperature. Međutim, ako pacijent nije pod sedacijom, zadata vrednost TT se ne menja, pa fizičko hlađenje može stoga izazvati hladnu reakciju, poput drhtavice ili suženja krvnih sudova koja nije poželjna. U tom slučaju bilo bi teško smanjiti TT, a potrošnja kiseonika i minutna ventilacija mogu se povećati. Dok se ne objave rezultati velikih randomizovanih ispitivanja o efektima antipiretičke terapije na kritično bolesne pacijente, čini se da bi antipiretičku terapiju trebalo izvoditi u skladu sa situacijom i individualno za svakog pacijenta.

Zaključak

Niz novih saznanja iz oblasti perifernog hlađenja i temoregulacije može biti od velike koristi u svakodnevnoj kliničkoj praksi i može značajno uticati na trenutnu praksu koju zdravstveni radnici sprovode. U skladu sa tim, potrebno je podsticati istraživanja u ovoj oblasti, kako bi upravljanje povišenom TT bilo zasnovano na naučnim dokazima primenjivim u praksi.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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consciousness, and therefore, in order to ensure the patient's comfort and efficient cooling, shivering must be reduced by centrally active agents. In patients who have endovascular hypothermia, surface covering of skin can reduce the threshold of shivering and increase the patient's tolerance and comfort. The majority of data on the control of shivering come from the research on the control of shivering after anesthesia (10).

The application of antipyretics

In addition to the previously described physical cooling, antipyretics can also be used in the treatment of febrile patients. An antipyretic can lower the body temperature by reducing the threshold of body temperature control in the hypothalamus. There are two critical assumptions regarding the application of antipyretic therapy. One assumption is that a fever is at least partially harmful, while another assumption is that the suppression of febrility will reduce, if not eliminate, the harmful effects of fever. None of the above mentioned assumptions has been experimentally confirmed, but since high temperature is a common sign of infection, it is considered to be a clear signal of inflammation. The febrile response as a component of the febrile process implies a complex reaction of the organism to pathogens, which includes the rise in the body temperature mediated by the action of cytokines and the activation of numerous physiological, endocrine and immunological mechanisms.

Antipyretics include a group of drugs that inhibit the production of prostaglandins, which are produced by the action of cyclooxygenase (COX) enzymes. The inhibition of COX-1 causes adverse side effects, while the inhibition of COX-2 reduces the inflammation, fever, and pain (15). Antipyretics that are most frequently used in clinical practice for the treatment of hyperthermia are paracetamol, ibuprofen, diclofenac and naproxen, and in certain indications, naproxen. The reasons for the use of antipyretic therapy include relief of symptoms, reduction of morbidity and mortality, prevention of febrile seizures, reduction of cognitive impairment and reduction of complications caused by stroke or brain injuries. The application of antipyretic drugs is especially important for sedated patients. Sedation should suppress cold reactions, and therefore, sedation combined with physical cooling should be effective in lowering BT. However, if the patient is not sedated, the given value of body temperature is not changed, and therefore, physical cooling may cause a cold reaction, such as shivering or vasoconstriction, which is not desirable. In that case, it would be difficult to reduce the body temperature, and oxygen consumption and minute ventilation may increase. Until the results of large randomized trials on the effects of antipyretic therapy in critically ill patients are published, it seems that antipyretic therapy should be applied in accordance with the situation and individually for each patient.

Conclusion

A series of new findings in the field of peripheral cooling and thermoregulation can be of great use in daily clinical practice and can significantly influence the current practice which is carried out by healthcare workers. Accordingly, it is necessary to encourage the research in this area, so that the management of fever would be based on scientific evidence applicable in practice.

Competing interests

The authors declared no competing interests.

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