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Hypothermia and normothermia effects on mortality rate of cardiopulmonary bypass

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ABSTRACT

Introduction: Cardiopulmonary bypass is associated with higher risk of mortality and morbidity, thus it should be investigated regarding the major risk factors. Temperature management have a significant role in postoperative cerebral and neurological complications; however the optimum temperature during cardiopulmonary surgery is not certainly detected. This systematic review has investigated the differences between hypothermia and normothermia regarding postoperative mortality.

Method: PubMed was searched for the relevant articles. Only English language articles were included with no time limitation. Data regarding in-hospital patient deaths provided in each article mostly within 30 days after the surgery, were extracted and compared based on relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT).

Result: Totally, 28 articles were retrieved and extracted. The mortality rate was zero in hypothermic and normotehrmic groups of 8/28 included studies, thus the RRR, ARR, and NNT could not be calculated. There were no significant differences between investigated groups of each included studies regarding the patients' age, gender, and preoperative conditions.

Conclusions: No significant difference was obtained between two studied groups. Similar prevalence of death observed between hypothermic and normothermic groups might be due to the sample size of studies, or the subsequent cares performed in intensive care units that assist to reduce the postoperative mortality rate. According to the obtained results, both of these procedures might be similarly safe regarding mortality rate.

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Introduction

Cardiopulmonary bypass (CPB) is a high risk and the main treating strategy in patients with coronary artery and valvular heart complications. Cardiac surgery is associated with significant morbidities due to arrhythmias, bleeding, stroke, and neuropsychiatric complications (1).

Temperature management is a significant factor during surgeries, which affects the outcomes of the surgery, thus it should be investigated in patients with coronary artery disease (CAD) that are candidates for CPB to obtain the best results.

Hypothermia has been proposed almost 50 years

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ago as a beneficial strategy in patients undergoing open heart surgery to reduce the consequent myocardial complications and to increase the myocardial protection during surgery. Hypothermia is known as an important approach which decreases cerebral oxygen demand and maintains blood flow in the central nervous system (CNS) during cerebral ischemia occurring in cardiac surgery (2).

Although CPB is conducted based on hypothermia with considerable successful results, various systemic adverse effects are reported to be associated with this surgical temperature including compromised drug metabolism, diaphragmatic dysfunction, long recovery time after anesthesia, cardiac complications, coagulopathy, wound infections, and postoperative shivering (3). Therefore, normothermia might be able to decrease the incidence of mentioned risks; however this method also elevates the possibility of cerebral and neurological complications. The exact advantages and disadvantages of each method are uncertain and under the investigation.

Methods

Literature search

PubMed was searched for the relevant articles with the following search term: hypotherm* AND normotherm* AND coronary AND (death OR mortality). Irrelevant articles were excluded after studying titles and abstracts following the initial search. The full text of the remaining articles was then studied. Reference lists of the included articles were searched to prevent missing any relevant article.

Study selection

Inclusion criteria were any randomized clinical trial which compared hypothermia with normothermia in patients undergoing CPB, induced cardioplagia, and provided data about the in-hospital death of patients after the surgery. Only English language articles were included in this systematic review. Relevant articles were extracted with no time limitation. Exclusion criteria were retrospective cohort and prospective studies, and case reports. Articles which induced mild hypothermia and the rewarmed patients were also excluded from the results.

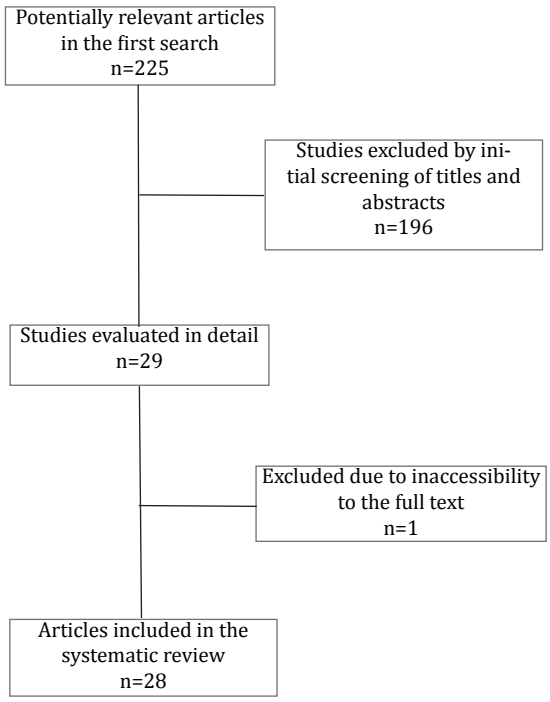
Data extraction

We excluded the patients who were died after the cardiac surgery in hypothermic and normothermic groups. In-hospital death or perioperative death were considered as mortality event in each group. Relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) were calculated according to the number of death in each group.

Results

Overall, 225 articles were identified through the initial search in PubMed; 196 articles were excluded from the results after studying titles and abstracts of the articles. Finally, 29 articles remained as the most relevant articles with the purpose of this study. One article was also excluded due to inaccessibility to full text for retrieving the event rate. The process of inclusion and exclusion pattern of the articles is revealed in Figure 1. Quality assessment of the results is provided in Table 1.

Figure 1. PRISMA flow chart of the study



Only one out of 28 included studies specifically investigated the mortality following coronary bypass with hypothermic condition compared with normothermic as its primary outcome. In other studies, mortality rate was reported as the secondary outcome.

The mortality rate was zero in hypothermic and normotehrmic groups of 28/8 included studies, thus RRR, ARR, and NNT could not be calculated in these studies. The calculated RRR, ARR, and NNT for the remaining 20 articles are provided in Table 2. There were no significant differences between investigated groups of each included study regarding the patients' age, gender, and preoperative conditions.

Table 1. Quality assessment of the included study

Author Year	Was the assignment of patients to treatments randomised?	Were the groups similar at the beginning of the trial?	A side from the allocated treatment, were groups treated equally?	Were all patients who entered the trial accounted?
Lomivorotov 2014	Computer-generated randomization list	Yes	Yes	Yes
Codispoti 2006	NA	Yes	Yes	Yes
Nathan 2004	Computer-generated randomization list	Yes	Yes	Yes
Gaudino 2002	Adequate concealment	Yes	Yes	Yes
Grimm 2000	NA	Yes	Yes	Yes
Parody 2000	NA	Yes	Yes	Yes
Jacquet 1999	NA	Yes	Yes	Yes
Ranucci 1997	NA	Yes	Yes	Yes
Chello 1997	NA	Yes	Yes	Yes
Birdi 1997	Card allocation into each group	Yes	Yes	Yes
Plourde 1997	Adequate concealment	Yes	Yes	Yes
Boldt 1996	NA	Yes	Yes	Yes
Regragui 1996	Adequate concealment	Yes	Yes	Yes
Anderson 1995	NA	NA	NA	NA
Arom 1995	NA	Yes	Yes	Yes
Christenson 1995	NA	NA	NA	NA
Naylor 1994	Sealed envelope	Yes	Yes	Yes
Martin 1994	Computer-generated randomization List	Yes	Yes	Yes
Lajos 1993	NA	Yes	Yes	Yes

NA: Not available

Discussion

Compared with normothermic temperature, hypothermia is considered to be beneficial in reducing the possibility of brain and other tissue injuries and ischemia. The incidence rate of ischemia and the following permanent damages might be higher during normothermic temperature surgeries (26).

For estimating the risk and advantages of temperature adjustment for CPB, it is essential to consider and compare various clinical variables. Clinical variables mostly studied in articles were

Table 2. Data extracted from the included articles

Author Year Reference	Patients	Perioperative mortality (Gr[1]1:Gr2)	RRR[2], 95%CI ARR[3] NNT[4]
Lomivorotov 2014 (4)	Total number: 140 CPB[5] 80m[6]:60F[7] Gr1: hypothermic(T=31-32°C) n[8]= 70 Gr2: normothermic (T >36°C) n= 72	1:1	RRR:0%, -276%-100% ARR:0.000, -0.039-0.039 NNT:NA[9]
Codispoti 2006 (5)	Total number:104 Gr1: hypothermic 31-32°C:n=52 G2:normothermic 37°C:n=52	0:0	NA
Nathan, 2004 (6)	Total number:144 CABG[10] age> 60 years old Gr1: hypothermic(34°C):n=71 Gr1:normothermic(37°C):n=73	2:0	RRR: NA ARR: -0.028, -0.066 to 0.010 NNT: -36
Gaudino 2002 (7)	Total number:113 elective CABG Gr1:hypothermic26°C:n=58 Gr2:normothermic37°C:n=55	2:0	RRR: NA ARR: -0.034, -0.081 to 0.013 NNT: -26
Grimm 2000 (8)	Total number: 144 elective CABG, mean age 62.1 ± 6.3 years Gr1:Hypothermic (32°C): n=72 Gr2:Normothermic(37°C): n=72	3:2	RRR: -50%, -264% to 100% ARR: -0.014, -0.076 to 0.046 NNT: -71
Parodi 2000 (9)	Total number:132 CABG and valvular surgery Gr1:hypothermic(26-30°C), n=66 Gr2:normothermic(-), n=66	2:2	RRR:0%, -194%-100% ARR:0.000, -0.039-0.039 NNT:NA
Jacquet 1999 (10)	Total number:200 for isolated coronary bypass Gr1:hypothermic30°C:n=92 Gr2:normothermic36°C, n=108	3:3	RRR:0%, -276%-100% ARR:0.000, -0.058-0.058 NNT:NA
Chello 1997 (11)	Total number:40 patients for elective coronary revascularization Gr1:hypothermic(25-28°C), n=20 Gr2:normothermic(37°C), n=20	0:0	NA
Ranucci 1997 (12)	Total number:50 patients for elective coronary revascularization Gr1:hypothermic:28°C:n=25 Gr2:normothermic:36°C:n=25	2:0	RRR: NA ARR: -0.080, -0.186-0.026 NNT: -13
Birdi 1997 (13)	Total number: 300 CABG Gr1:hypothermia(28°C), n=100 Gr2:normothermia(37°C), n=100	2:1	RRR:-100%, -437%to100% ARR:-0.010, -0.044-0.024 NNT:-100
Plourde 1997 (14)	Total number: 54 Gr1:hypothermia(28°C), n=24 Gr2:normothermia(36C), n=30	0:0	NA
Boldt 1996 (15)	Total number: 54 Gr1:hypothermia(28°C), n=15 Gr2:normothermia(36C), n=15	0:0	NA
Regragui 1996 (16)	Total number: 54 Gr1:hypothermia(28°C), n=36 Gr2:normothermia(36C), n=29	0:1	RRR:100%, -276%-100% ARR:0.034, -0.032-0.010 NNT:29
Anderson 1995 (17)	Total number:20 patients Gr1:hypothermia(-),n=12 Gr2:normothermia(-)n=8	0:0	NA
Tonz 1995 (18)	Total number:30 patients Gr1:hypothermia(28°C),n=16 Gr2:normothermia(36°C)n=14	0:0	NA
Christenson 1995 (19)	Total number: 1442 CABG Gr1:hypothermia(28°C), n=545 Gr2:normothermia(37°C), n=897	18:23	RRR: -27%, -976% to 43% ARR: -0.007, -0.025 to 0.011 NNT:-143

Author Year Reference	Patients	Perioperative mortality (Gr1:Gr2)	RRR, 95%CI ARR NNT
Maccherini 1995 (20)	Total number: 100 CABG Gr1:hypothermia(28°C), n=50 Gr2:normothermia(37°C), n=50	1:2	RRR:50%, -117%-100% ARR:0.020, -0.047-0.087 NNT:50
Kaukoranta 1995 (21)	Total number: 101 CABG Gr1:hypothermia(32-33°C), n=50 Gr2:normothermia(37°C), n=51	1:0	RRR:NA ARR:-0.020, -0.059-0.016 NNT:-50
Arom 1995 (22)	Total number: 1442 CABG Gr1:hypothermia(34°C), n=100 Gr2:normothermia(37°C), n=100	4:3	RRR:-330%, -203%-100% ARR:-0.000, -0.061-0.041 NNT:-100
Rashid 1995 (23)	Total number:108 Gr1:hypothermia(28°C),n=50 Gr2:normothermia(36-37°C),n=58	2:0	RRR:NA ARR:-0.040, -0.094-0.014 NNT:-25
Naylor 1994 (24)	Total number:1732 Gr1:hypothermia(25-30°C),n=872 Gr2:normothermia(33-37°C),n=860	22:12	RRR: -79%, -171% to14% ARR: -0.011, -0.024 to 0.002 NNT: -91
Rashid 1994 (25)	Total number:281 Gr1:hypothermia(28°C), n=144 Gr2:normothermia(37°C), n=137	1:3	RRR:68%, -59%-100% ARR:0.015, -0.013-0.043 NNT:67
Martin 1994 (26)	Total number: 1,001 CABG patients Gr1:hypothermia(≤28°C), n=508 Gr2:normothermia(≥35°C), n=493	8:5	RRR: -6%, -200% to 80% ARR: -0.06, -0.020 to 0.008 NNT: -167
Cook 1994 (2)	Total number: 52 CABG Gr1:hypothermia(27°C), n=26 Gr2:normothermia(37°C), n=26	0:1	RRR:100%, -59%-100% ARR:0.038, -0.035-0.111 NNT:26
Boldt 1994 (15)	Total number: 1,001 CABG patients Gr1:hypothermia(29°C), n=15 Gr2:normothermia(36°C), n=15	0:0	NA
Lajos 1993 (27)	Total number: 109 CABG patients Gr1:hypothermia(30°C), n=55 Gr2:normothermia(36-37°C), n=54	2:0	RRR:NA ARR:-0.036, -0.085-0.013 NNT:-28
Bert 1993 (28)	Total number: 30 CABG Gr1:hypothermia(25-26°C), n=14 Gr2:normothermia(36-38°C), n=16	0:0	NA
Lehot 1992 (29)	Total number: 20 CABG patients Gr1:hypothermia(25°C), n=10 Gr2:normothermia(37°C), n=10	0:1	RRR:100%, -59%-100% ARR:0.100, -0.086-0.286 NNT:10

[1]Gr: group; [2]RRR: relative risk reduction; [3]ARR: absolute risk reduction; [4]NNT: number needed to treat; [5]CPB: cardiopulmonary bypass; [6]M: male; [7]F: female; [8]n: number; [9]NA: not available; [10]CABG:coronary artery bypass grafting.

cerebral, myocardial, and renal complications, in-hospital stay duration, blood transfusion requirement, and bleeding.

The mortality rate of patient candidate for CPB under the normothermic condition compare with hypothermic, has not been studied before. According to experimental studies, hypothermia has a definite cardioprotective effect, but the results of clinical studies indicate otherwise.

Based on results obtained in one previous systematic review and meta-analysis performed by Rees et al. in 2001, there was a statistically non-significant difference between hypothermic and normothermic methods regarding the perioperative mortality rate; however the hypothermic approach was associated with higher number of non-stroke perioperative death. The estimated Odds ratio (OR) was 1.46 [0.90, 2.37] in hypothermic versus normothermic methods. Data in that systematic review was extracted from 16 studies investigated total of 4201 patients and the revealed information was about perioperative deaths not caused by stroke (30). In that systematic review the follow-up duration was within 30 days after the surgery.

Only 1 out of 28 included trials, specifically studied the mortality rate following hypothermia condition compared with normothermia in patients undergoing aorto-coronary bypass surgery in a large sample size clinical trial conducted in three center in 1994. In this study, randomization was performed by envelope method. The follow-up du

ration was 30 days (26).

Mortality rate is an important factor that could change the treating approach under CPB surgery. According to articles, in-hospital mortality is defined as death during the hospital stay. Based on included studies nasopharyngeal and rectal temperature probe was the most reliable indicator of brain temperature.

Based on included studies in present systematic review, death occurred due to various reasons including cardiogenic shock following perioperative myocardial infarction at the day of surgery, hyposensitivity and not being resuscitated, low cardiac output and cerebral infarction, sudden death on postoperative day. In one study in 1994, patients death were screened in two different categories including deaths caused by myocardial infarction or ischemia (refractory cognitive hearth failure without postoperative myocardial infarction), and deaths caused by other reasons related to ischemia (sepsis, multiorgan failure following prolonged ventilation) or not related to cardiac events (24).

Another article studied the effect of postoperative hypothermia on patients underwent CABG regarding incidence of death. In this study, in patients with intensive care unit (ICU) admission, temperature lower than 36°C considerably had a higher mortality rate compared with normothermic patients; odds ratio, 0.59; 95% confidence interval, 0.39-0.91). Therefore, they concluded that patients who arrived at ICU with normal temperature were at lower risk of in-hospital mortality. Totally, their results showed that there was not a considerable difference between hypothermia and normothermia considering the mortality rate. In this regard, mortality rate of these approaches is not high enough to change the chosen treating strategy in patients who are candidates for CABG. This non-significant difference between two studied approaches might be due to low sample size of the included studies or due to the treating strategies performed routinely in ICU following cardiac surgeries which reduce the death incidence.

Conclusion

Due to the small number of death among screened articles, clinical trials with larger sample sizes might be able to reveal the mortality rate difference between two surgical temperatures.

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Conflict of Interest

The authors declare no conflict of interest.

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