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HTK 液与冷血停搏液在心脏瓣膜手术中应用对比:倾向得分匹配分析*

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摘要 目的:比较 HTK 液与冷血停搏液在心脏瓣膜手术中应用效果,为临床心肌保护灌注策略提供依据。**方法:**采用单中心数据回顾性分析,选取 2015 年 5 月-2018 年 8 月在体外循环下(CPB, Cardiopulmonary Bypass)应用灌注停跳液停跳的瓣膜手术患者 529 例,分为冷停液组(n=326)及 HTK 液组(n=203),采用倾向得分匹配方法将上述两组资料进行匹配,确定选取 73 对可匹配病例进行比较。采集的临床结果主要为 CPB 时间,阻断时间,ICU 停留时间(intensive care unit length of stay, ICU LOS)以及血清钠术中术后浓度变化等参数。其次为,术后呼吸机辅助时间,IABP(Intra aortic ballon pump)的使用及新发透析,30 天死亡率与术后主要并发症情况。**结果:**匹配后两组中冷停液组较 HTK 液组的主动脉平均阻断时间及 CPB 时间长,差异具有统计学意义($P<0.05$),HTK 液组存在短暂性低血钠血症($P<0.05$),ICU LOS 以及其余各临床结果无显著差异。**结论:**心脏瓣膜手术中应用 HTK 液与冷血停搏液临床早期结果一致,可根据手术操作流程及病人经济水平进行合理选择。

关键词:体外循环;心肌保护液;心脏瓣膜手术;倾向得分匹配分析

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Histidine-Tryptophan-Ketoglutarate Solution Versus Cold Blood Cardioplegia in Cardiac Valve Surgery: A Propensity-Score Matched Analysis*

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ABSTRACT Objective: To compare the effects of Histidine-Tryptophan-Ketoglutarate Solution and Cold blood cardioplegia in valve surgery, and provide evidence for clinical myocardial protection perfusion strategy. **Methods:** A retrospective analysis of single-center data was used to select 529 patients with valve surgery who underwent cardiopulmonary bypass (CPB) from May 2015 to August 2018. Divided into cold blood cardioplegia group (n=326) and HTK solution group (n=203). Propensity score matching was used to adjust for differences between the two groups, and 73 matched pairs were identified. The primary end point was CPB time, aortic block time, ICU (intensive care unit) length of stay (LOS), and intraoperative changes in serum sodium concentration. Secondary end point included postoperative ventilator assist time, the use of IABP (Intraaortic ballon pump) and new dialysis, 30-day mortality and major postoperative complications. **Results:** For the matched, the average aortic block time and CPB time of the cold blood cardioplegia group was longer than HTK solution group, and the difference was statistically significant ($P<0.05$). There was acute transient hyponatremia in the HTK group ($P<0.05$), and there was no significant difference in ICU LOS and other clinical outcomes. **Conclusions:** During cardiac valve surgery, both cardioplegia techniques were consistent in the early clinical results, which can be selected according to the surgical procedure and the patient's economic level.

Key words: Cardiopulmonary bypass (CPB); Myocardial cardioplegia; Cardiac valve surgery; Propensity score matching analysis

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前言

心肌保护是现代心脏外科重要组成部分之一,其中灌注停跳液是心肌保护的重要措施。经冠状动脉灌注停跳液保存心肌细胞的能量储备,减少心肌代谢率以避免心肌细胞的渗透压,电解质及 pH 值的紊乱^[1]。目前使用的心脏停搏液根据含有

的电解质成分可分为两类:细胞外型及细胞内型停跳液^[2]。其中 St.Thomas NO.2 溶液^[3]是目前各国心脏中心使用最广泛的细胞外型停搏液,通常用患者自体血作为载体每 20-30 分钟灌注一次^[4],具有价格低廉和安全高等特点。而属于细胞内型的 HTK 液^[5]临床认为一次灌注可提供长达 3 小时足够的心肌保护,同时对成人及幼儿体外循环后器官功能起保护作用^[6-8],极大地提

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高了术程流畅性。HTK 液不仅可作为灌注停搏液,还可用于移植手术中的器官保存液^[9,10],但 HTK 液属于进口药品,导致其价格较为高昂。随着近几年国内外关于停跳液研究的深入,很多科研工作者对两种停跳液在心脏手术中的心肌保护效果进行了分析和对比,但研究结果依然存在较大的分歧。本研究所选取的样本均位于高寒边疆地区,具有瓣膜疾病发病率高、病患病史长及术前心功差等特点。使得重症心脏瓣膜手术在总体手术量中占比较大,因此术中心肌保护尤为重要,当前我中心在心脏手术中使用以上两种类型停跳液进行心肌保护。根据病患手术中使用的停搏液类型进行大数据回顾性分析,为保证数据可比性通过倾向得分匹配分析方法比较在成人瓣膜手术中应用 HTK 液与冷血停跳液中术后效果,为今后的瓣膜手术提供心肌保护灌注策略。

1 资料与方法

1.1 临床资料

选取 2015 年 5 月-2018 年 8 月在体外循环下行心脏瓣膜手术病人的临床资料。入组标准:成人体外循环下的瓣膜疾病,包括风湿性心脏病,感染性心内膜炎及退行性瓣膜病,手术种类有主动脉瓣置换手术(AVR)、二尖瓣置换手术(MVR)、双瓣置换手术(DVR),合并三尖瓣成形术/置换术(TVP/TVR)、冠状动脉移植旁路(CABG)手术以及赘生物及血栓清除术。涉及到合并大血管(升主动脉及主动脉弓)的手术被排除在外。根据停搏液的使用类型分为 HTK 液组 326 例及冷停液组 203 例,运用倾向得分匹配方法将 529 例病患的术前术中资料进行匹配,从中选择可匹配病例进行术中术后结果对比。经倾向匹配评分后,HTK 组 73 例病患及冷停液组 73 例病患可入组匹配。选择使用 HTK 液和冷血停搏液(病患自体血 4:1 混合 St. Thomas NO.2 溶液)的标准根据体外循环医师及外科术者的偏好以及手术进程的特点决定。

1.2 体外循环方法和心肌保护

麻醉给予芬太尼、咪达唑仑、丙泊酚、泮库溴铵和异氟醚静吸复合麻醉,患者经动脉管路与中心静脉测压,并选择性的进行食道超声监测。全身肝素化抗凝大于 480 秒,升主动脉插管或股动脉插管建立体外循环,通过腔房管、上下腔静脉或股静

脉进行静脉引流,体温维持 30 至 33 度之间。主动脉阻断后,经从主动脉根部或者左右冠状动脉灌注冷血停跳液或 HTK 液(4-8 度)进行心肌保护。冷血停跳液首次灌注 10-15 mL/kg,灌注压力 120-150 mmHg 灌入冠状动脉口,停跳后以 5-8 mL/kg 顺行灌注 3-5 分钟,并每间隔 20-30 分钟复灌一次半剂量。HTK 液单次主动脉根部灌注 1.5-2L,压力维持在 80-100 mmhg 灌注 5-7 分钟,可维持 3 小时主动脉阻断期间的心肌保护效果。

1.3 临床数据资料采集

采集的数据主要为术中与术后早期临床结果:ICU 停留时间、主动脉阻断时间、CPB 时间、血清钠浓度变化、呼吸机辅助时间和术后主要并发症的发生率(包括术后急性肾损伤、中风、重新开胸止血和术后安置 IABP)与 30 天死亡率。

1.4 统计分析方法

通过均数±标准差(SD)或中数来描述持续变量,通过百分比(%)来描述绝对变量。两组计量资料通过 t 检验,两组不同时间点的计量资料通过逻辑模型或方差分析(ANCOVA)。计数资料通过 χ^2 检验。采用倾向得分匹配分析方法(P propensity Score Matched Analysis)是运用逻辑回归模型消除不匹配组病患术前数据差异,包括:年龄、性别、体表面积、合并高血压、糖尿病、血脂异常及陈旧性心肌梗死、充血性心衰、慢性肺病、脑血管疾病,NYH 分级,射血分数,肌酐,红细胞压积,是否进行了二次手术。根据倾向得分选择合适病例进行匹配。所有数据分析是应用 SAS 9.4 软件统计分析。 $P \leq 0.05$ 视为有统计学意义。

2 结果

2.1 倾向匹配前两组特征及临床结果

研究期间,共有 529 例瓣膜手术患者在体外循环下应用灌注停跳液进行心肌保护,其中 HTK 液组 326 例,冷停组 203 例。倾向匹配前两组病患术前资料对比结果见于表 1,表现为冷停组病患年龄较大,性别组成男性居多,血脂异常,高血压,糖尿病发病率较 HTK 组高。充血性心衰、肌酐高值、射血分数值略低及二次手术百分比在 HTK 组中更普遍($P < 0.05$)。HTK 液更多用于双瓣手术及瓣膜+CABG 手术,单瓣置换手术则优先选用了冷血停跳液($P < 0.05$)。

表 1 匹配前 HTK 组与冷停组患者术前术中资料数据

Table 1 Preoperative and Operative Patients's Characteristics before the matched

Variable	Blood Cardioplegia(n=326)	HTK Solution (n=203)	P
Age(year)	60.6± 12.8	55.9± 13.1	< .001
Male gender(%)	229(70.0)	120(59.1)	< .001
BMI	25.7± 4.4	25.1± 4.4	.001
Hypertension	199(61.0)	101(49.7)	< .001
Diabetes	43(13.1)	13(6.4)	< .001
Dyslipidemia	125(38.3)	35(17.2)	< .001
Myocardial inarction	110(33.7)	22(10.8)	< .001
CHF	32(9.8)	38(18.7)	< .001
Cerebrovascular	12(3.6)	10(4.9)	.05
COPD	23(7.0)	15(7.3)	.834

EF%	49.1± 13.1	51.0± 12.9	.024
Creatinine(mg/dL)	1.03± 1.6	1.15± 1.6	.008
Hematocrit(%)	41.7± 6.6	42.0± 7.0	.150
NYHA functional class			
I	12(3.6)	6(2.9)	< .001
II	56(17.1)	47(23.1)	< .001
III	224(68.7)	128(63.0)	< .001
IV	34(10.4)	22(10.8)	< .001
Redo operation	6(1.8)	11(5.4)	< .001
Type of surgery			
AVR	72 (22)	17 (8.3)	< .001
MVR	154(47)	22(10.8)	< .001
DVR	13(3.9)	28(13.7)	2
+TVP/TVR	40(12.2)	32(15.7)	.048
+CABG	38(11.6)	92(45.3)	< .001
+Thrombectomy	11(3.3)	12(5.9)	.137

Note: Data are presented as mean± standard deviation or n (%). BMI, body mass index; CHF, indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; NYHA, New York Heart Association; CABG, coronary artery bypass grafting;

2.2 倾向匹配后两组特征及临床结果

73 例患者临床资料列入匹配组进行比较。通过表 2 表明,匹配

倾向得分匹配后,确定冷停液组的 73 例患者与 HTK 组的 73 例患者术前各项数据间没有明显统计学差异。

表 2 匹配后 HTK 组与冷停组患者术前术中资料数据

Table 2 Preoperative and Operative Characteristics for the Matched Patients

Variable	Blood Cardioplegia(n=73)	HTK Solution (n=73)	P
Age(year)	58.8± 15	57.9± 15	.903
Male gender(%)	47(63.4)	43(58.9)	.090
BMI	26.1± 4	25.5± 4	.116
Hypertension	40(54.7)	39(53.4)	.611
Diabetes	6(8.2)	7(9.5)	.899
Dyslipidemia	16(21.9)	13(17.8)	.061
Myocardial inarction	10(13.6)	7(9.5)	.068
CHF	14(19.1)	16(21.9)	.602
Cerebrovascular	3(4.1)	4(5.4)	.896
COPD	5(6.8)	4(5.4)	.977
EF(%)	49.0± 13.1	50.7± 12.9	.179
Creatinine(mg/dL)	1.01± 0.8	1.13± 1.0	.181
Hematocrit(%)	41.5± 7.4	40.9± 7.0	.691
NYHA functional class			
I	2(2.7)	1(1.4)	.824
II	11(15.0)	10(13.6)	.917
III	46(63.0)	48(65.7)	.734
IV	14(19.1)	13(17.8)	.604
Redo operation	2(2.7)	1(1.3)	.926
Type of surgery			
AVR	20 (27.3)	18 (24.2)	.741

MVR	17(23.2)	14(19.1)	.562
DVR	9(12.3)	13(17.8)	.074
+TVP/TVR	14(19.1)	11(15.0)	.248
+CABG	11(15.0)	14(19.1)	.248
+Thrombectomy	2(2.7)	3(4.1)	.824

Data are presented as mean $\pm$ standard deviation or n (%). BMI, body mass index; CHF, indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; NYHA, New York Heart Association; CABG, coronary artery bypass grafting;

比较结果表 3 显示,HTK 液组术中主动脉阻断时间及 CPB 时间较冷停液组更短,具有统计学差异($P<0.05$)。其次观察停跳液灌注后,HTK 组血钠浓度明显降低($P<0.05$),但术后

第一天即可恢复正常值。两组 ICU 停留时间及其余各临床指标间无显著差异。

表 3 匹配组术中术后临床结果

Table 3 Operative and Clinical Outcomes for the Matched Patients

Variable	Blood Cardioplegia(n=73)	HTK Solution (n=73)	P
CPB time(min)	149.9 $\pm$ 44.3	132.6 $\pm$ 52.8	.001
Aortic cross-clamp(min)	115.6 $\pm$ 24.9	95.7 $\pm$ 31.2	< .001
Intraoperative sodium(mmol/L)			
Before CPB	140.2 $\pm$ 4.0	140.4 $\pm$ 3.8	.238
After cardioplegia	136.4 $\pm$ 3.7	135.5 $\pm$ 3.6	< .001
Final CPB	138.7 $\pm$ 4.0	139.2 $\pm$ 3.3	< .001
ICU day 1	139.5 $\pm$ 3.1	130 $\pm$ 5.7	.712
ICU LOS(days)	6.23 $\pm$ 4	6.12 $\pm$ 4	.685
IABP use	4(5.4)	3(4.1)	.896
Clinical stroke	1(1.4)	1(1.4)	>.999
Prolonged(>24 h)ventilation	8(10.9)	10(13.6)	.756
New onset dialysis	2(2.7)	3(4.1)	.824
Reexploration for bleeding	3(4.1)	1(1.4)	.714
30 day mortality	2(2.7)	1(1.4)	.824

Data are presented as mean $\pm$ standard deviation or n (%); CPB: cardiopulmonary bypass time;

ICU LOS: intensive care unit length of stay; IABP: Intraortic balloon pump.

3 讨论

停跳液的使用是心脏手术中对心肌保护最重要的措施之一,在许多国家的心脏中心都在常规性地使用冷血停跳液进行间歇性灌注来达到对心肌保护要求的安全范围。而随着心脏微创手术及其他复杂技术的持续快速发展,使得通过单次灌注即可获得长时间心肌保护的灌注液(例如 HTK 液)逐渐吸引起临床工作者的兴趣^[11]。近期对 DelNido 停跳液前瞻性研究显示,其具有良好的心肌保护效果的同时可以简化手术进程,并逐渐开始探索将其应用于成人心脏手术^[12,13]。最新报道的改良全血微晶体停跳液,作为新型心肌保护策略被成功应用在高危心脏手术中,并已获得良好的早期临床结果^[14]。由于目前停跳液的种类复杂,灌注方式也不尽相同,因此不同灌注停跳液对心肌保护的效果仍然存在许多的争论。

Aaersaeth 等^[15]在对单次灌注 HTK 液与间歇多次灌注冷血停跳液进行比较研究:在实验猪身上建立心肌保护模型,结果发现实施冷血停跳液灌注对左心室收缩的保护能力要优于 HTK 液灌注,但这些实验结果的优越性从未在临床研究中得

到证实。Wiesenack 等^[16]设计对比了在冠脉搭桥手术(CABG)中使用 mini 体外循环管道分别顺行灌注冷血停跳液与灌注 HTK 液效果,结果显示临床结果无明显差异。虽然冷血停跳液组的术后并发症发生率稍低,但可能是由于 mini 体外循环管道带来的优势所影响。而另一些研究认为在常规 CABG 手术中应用以上两种停跳液对比结果间没有明显差异^[17]。这两类停跳液的心肌保护对比在心脏微创手术中同样也有研究,临床结果相同^[18]。但同时显示长时间心脏停搏的瓣膜微创手术中 HTK 液能提供出色的肌保护作用,降低了重复灌注与灌注针头移位导致的冠状动脉灌注不足的风险^[19,20],近年也有涉及在小儿先天性心脏病^[21]及重症瓣膜手术中进行两种停跳液的应用效果对比,结果显示两者间差异不明显^[22]或 HTK 液在术后某些心肌保护指标上具有一定优势^[23,24]。在采用倾向得分匹配方法所进行的对比研究结果中,HTK 液与冷血停跳液在心脏动脉大血管手术中的心肌保护具有同样的安全性与有效性^[25]。虽然以上各方报道所得出的结论存在一定的分歧,但所有研究都均强调了在心脏手术中应用 HTK 液单次灌注的简便性。

同时,也有将重点聚焦在应用 HTK 液时由于血液稀释及

低钠成分造成的低钠血症的有害影响^[26],以及因纠正低血钠而快速补充钠离子带来的危害^[27,28]。近期一些报道认为,短暂的低钠血症的发生经常在 HTK 液灌注后出现,但其临床相关性很小,因为低钠现象在没有进行特殊的治疗干预下会随着体外循环结束而恢复到正常水平^[29]。此次对比结果印证了以上研究结论。

本研究通过倾向匹配分析,显示冷停组的 CPB 时间及主动脉阻断时间更长,因为相比较灌注 HTK 液而言,由于冷血停跳液灌注间隔时间较短且需多次灌注导致了整体手术进程的延长;其次,我中心采用的是 Arslan^[30]推荐的低剂量灌注策略,即 HTK 液总灌注剂量约为 15 mL/kg (多数文章传统推荐量为 20-25 mL/kg),因此灌注时间相应也减少了 2-3 分钟。

综上所述,回顾性分析结论认为,在较大人群的心脏瓣膜病手术中,即使术中使用冷血停跳液灌注会延长主动脉阻断时间与 CPB 时间,但应用 HTK 液与冷血停跳液在早期临床结果是一致的。术后的 ICU 停留时间,机械通气时间,术后并发症的发生率以及 30 天内死亡率等参数在这两种灌注液应用比较中也没有明显统计学差异。但在实际临床应用中,单次灌注 HTK 可以显著简化手术操作,避免多次灌注对冠脉口损伤的风险并增加外科医生在手术过程的舒适度,对于合并主动脉瓣疾病与冠脉血管病变具有保护意义。但冷血停跳液灌注安全,价格低廉更加适合本地区经济水平。可根据患者经济状况及手术类型选择适合的停搏液。

局限:本文是对瓣膜手术中应用两种停跳液的一个较大人群数据的回顾对比研究,虽然采取了倾向得分匹配的方法来最小化术前的数据差异,但单中心数据回顾存在着自身设计局限:主动脉开放后室颤是否发生,无术后射血分数及心肌酶值的测定。需要进一步深入研究。

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