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REVIEW ARTICLE

Del Nido cardioplegia versus other contemporary solutions for myocardial protection – a literature review

Barbara Brzeska, Wojtek Karolak, Paweł Żelechowski, Andrzej Łoś, Nikodem Ulatowski, Rafał Pawlaczyk

Department of Cardiac & Vascular Surgery, Medical University of Gdańsk, Poland

Abstract

Myocardial protection is one of the most important factors ensuring patient safety during cardiac surgery with the application of cardiopulmonary bypass. Infusion of cardioplegic solution into the coronary circulation protects the heart and provides a standstill operating field for the surgeon. Cold blood cardioplegia and crystalloid cardioplegia are the two main types of solutions with a long history of use and a large amount of research proving their efficacy and safety. Relatively new del Nido cardioplegia seems to be an interesting alternative. We reviewed the literature comparing del Nido cardioplegia with two other types of cardioplegic solutions. We took into consideration many different clinical and biochemical aspects may indicate the quality of cardioprotection.

Keywords: cardiac surgery · cardioprotection · del Nido cardioplegia · cold blood cardioplegia · Bretschneider HTK cardioplegia

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Introduction

Effective myocardial protection is crucial for a successful outcome of cardiac surgery with the application of cardiopulmonary bypass (CPB). For nearly 50 years the most common method of cardioprotection has been the infusion of cardioplegic solution into the coronary vessels. This provides a bloodless and motionless operating field which is perfect for precise surgery, however with a time limit resulting from the principles of physiology and biochemistry. The safe ischemic time varies depending on the composition and temperature of the cardioplegic solution. Some of the warm

Corresponding author:
Barbara Brzeska, Department of Cardiac & Vascular Surgery, Medical University of Gdańsk, Poland
e-mail: brzeska.bar@gumed.edu.pl
Available online: www.ejtcm.gumed.edu.pl

blood infusions must be delivered continuously, whereas a single infusion of some cold crystalloid solutions provide over two hours of secure myocardial protection during cross-clamping (XC) of the aorta. Thanks to research we have a much better understanding of the mechanism of ischemia-reperfusion injury (IRI) and better ways to prevent it.

Cardioplegia is a name given to a group of solutions using different mechanisms to arrest the heart in diastole with additives for cell membrane stabilization or oedema prevention. The mechanism of each is the result of a characteristic composition (Table 1). The development of high-potassium blood cardioplegia was a milestone in cardiac surgery. However, short intervals between doses are its weak point, particularly in the current era of minimally invasive cardiac procedures. Whereas the low-sodium crystalloid solution provides a very long working interval and rarely has to be re-dosed, however the long reperfusion time is a disadvantage. Del Nido cardioplegia (DNC) solution derived from pediatric cardiac surgery combines the most important aspects of the high-potassium and low-sodium cardioplegia solutions making it an interesting alternative for adult patients. Despite the growing number of studies and meta-analysis, there are no guidelines or consensus regarding which cardioplegic solution is the most beneficial.

Table 1. Cardioplegia solutions composition

Component	DNC	HTK	CBC
Na^{+} (mmol/l)	150	15	136-152
Cl^{-} (mmol/l)	132	50	126-132
K^{+} (mmol/l)	24	9	13-24
Mg^{2+} (mmol/l)	6	4	2-13
Ca^{2+} (mmol/l)	0.4	0.02	0-1
Lidocaine (mg/l)	140	-	27
Mannitol (mmol/l)	14.5	30	0-12
Osmolality (mOsmol/kg)	294	300	304-320
Ketoglutarate (mmol/l)	-	1	-
Tryptophan (mmol/l)	-	2	-
Histidine (mmol/l)	-	198	-

CBC – cold blood cardioplegia, DNC – Del Nido cardioplegia, HTK – Bretschneider histidine-tryptophan-ketoglutarate solution

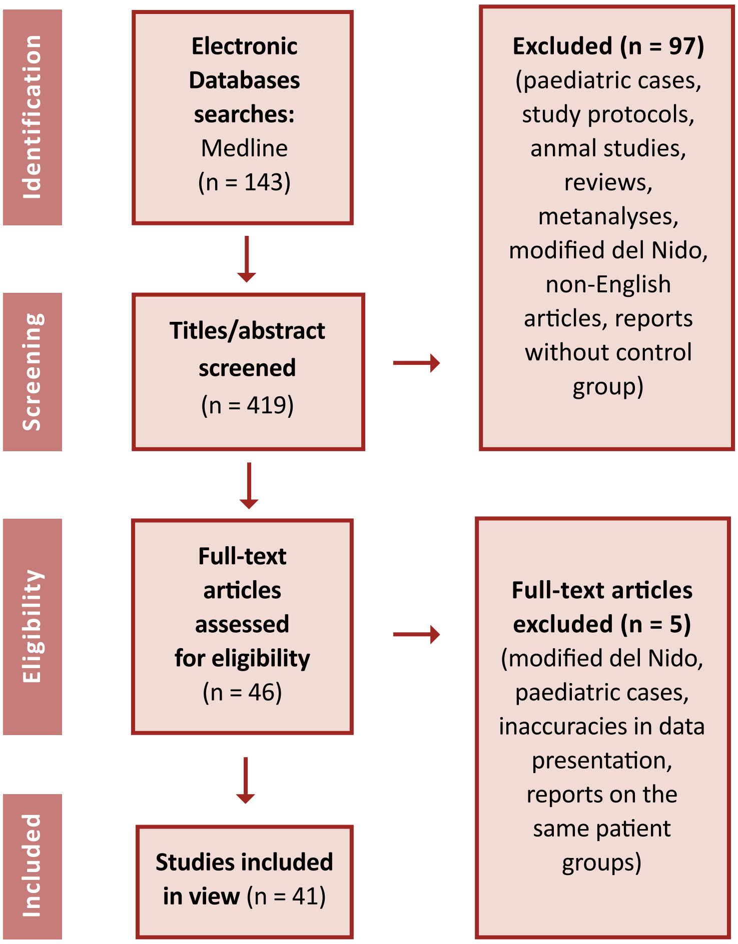

Figure 1. Literature search flow chart

Material and methods

For this review, we included retrospective and prospective studies comparing DNC with cold blood cardioplegia (CBC) of any kind or crystalloid cardioplegia (Bretschneider histidine-tryptophan-ketoglutarate solution (HTK)). We searched the MEDLINE database for English-language articles using the following keywords: "del Nido cardioplegia," "del Nido vs cardioplegia" and "cardioplegia AND del Nido". We looked for articles on standard adult cardiac procedures (single valve or coronary artery bypass grafting (CABG)) and combined procedures (multivalve, reoperations, aortic root). After evaluation of the substantive value of abstracts, full-text articles were analyzed. The analyzed studies concerned a total of 9839 cases, including 5073 with del Nido cardioplegia. Experimental, animal-model, pediatric and modified del Nido studies were excluded (Figure 1). Results from selected studies are collected and presented in the form of tables with an indication of the number of included patients, the type of surgery and study design (prospective, retrospective and retrospective with propensity-score matching (PSM)).

Results

Cardiopulmonary bypass and cross-clamp times

Significant shortening of the CPB and XC times in the DNC groups compared with CBC was described in most of the analyzed studies [1-17] (Table 2). Four studies [18-21] reported shorter XC times without a change in the CPB time. This may confirm that surgery is performed smoothly when DNC is used but may suggest the necessity of a longer reperfusion or lidocaine residual effect with delayed activation of the conductive system. Compared with HTK, there were no reported differences in CPB or XC times. This might be due to the fact that only one dose of cardioplegia was usually needed in both groups.

Table 2. CPB and XC times

Article	Cardioplegia	Study design	Cardiac procedures	No. of patients	CPB times [min]			p value	Cross clamp times			p value
					DN	BC	HTK		DN	BC	HTK	
Eris (2021)	DN vs BC	retrospective	aortic root procedures	118	114.4 ±27.1	123.9 ±28.8	-	0.071	73.3 ±20.7	87.5 ±23.2	-	**0.001**
Kagan (2021)	DN vs BC	retrospective	CABG	350	90.28 ±25.56	93.56 ±24.78	-	0.175	57.75 ±16.96	63.56 ±18.45	-	**0.014**
Lama (2021)	DN vs BC	RCT	CABG	90	106.13 ±24.65	107.62 ±18.69	-	**0.02**	66.22 ±15.39	72.07 ±12.23	-	**0.04**
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	163±5	181±5	-	**0.01**	145±4	161±4	-	**0.006**
Reidy (2021)	DN vs BC	retrospective	CABG in veterans	155	96.8 ±32.1	117.0 ±27.3	-	**< 0.01**	63.9 ±21.8	71.7 ±18.6	-	**0.02**
Ross (2021)	DN vs BC	retrospective	all cardiac procedures	497	96 (73-121)	96 (73-127)	-	0.82	67 (48-92)	63 (48-90)	-	0.63
Sanri (2021)	DN vs BC	retrospective	CABG	255	95.16 ±23.48	90.01 ±24.25	-	0.086	59.30 ±17.36	62.80 ±18.66	-	**0.042**
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	161.0 (153.2-170.7)	163.5 (156.0-175.5)	-	0.3	99.0 (94.2-106.0)	124.0 (117.0-131.0)	-	**< 0.001**
Shu (2021)	DN vs BC	PM	all cardiac procedures	326	111.0 (90.5-130.0)	106.0 (85.0-134.0)	-	0.422	75.0 (58.5-90.5)	73.0 (57.5-91.5)	-	0.564
Algarni (2020)	DN vs BC	retrospective	all cardiac procedures	305	150±51	178±60	-	**< 0.001**	118±42	143 ±60	-	< 0.001
Chen (2020)	DN vs BC	PM	acute aortic dissection	122	165.0 ±12.5	168.0 ±10.5	-	0.154	93.2 ±9.5	91.8 ±9.0	-	0.405
George (2020)	DN vs BC	PM	CABG or valve	286	90 (74-116)	87 (76-108)	-	0.516	59 (48-75)	57 (47-70)	-	0.65
Kirisci (2020)	DN vs BC	RCT	CABG	60	95.07 ±23.06	114.13 ±33.93	-	**0.01**	57.30 ±23.57	76.07 ±27.18	-	**0.01**
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	129.39 ±5.72	151.94 ±10.12	-	**0.001**	96.75 ±5.24	116.42 ±9.27	-	**0.001**
Orak (2020)	DN vs BC	retrospective	elective all cardiac procedures	83w	114.58 ±6.30	112.43 ±6.40	-	0.811	77.93 ±6.12	70.73 ±6.17	-	0.41
Schutz (2020)	DN vs BC	PM	CABG or CABG and valve	670	51.600 ±20.625	49.233 ±22.230	-	0.109	32.063 ±15.795	31.313 ±16.384	-	0.513
Sharma (2020)	DN vs BC	retrospective	AVR + MVR	209	92.1 ±12.3	129.5 ±11.0	-	**0.0001**	72.6 ±10.2	98.2 ±9.2	-	**0.0001**

Table 2. continuation

Article	Cardio-plegia	Study design	Cardiac procedures	No. of pa-tients	CPB times [min]			p value	Cross clamp times			p value
					DN	BC	HTK		DN	BC	HTK	
Ucak (2020)	DN vs BC	retro-spective	AVR	137	53.7 ±15.2	60.8 ±18.5	-	**0.046**	41.5 ±11.8	48.7 ±12.3	-	**0.041**
Willekes (2020)	DN vs BC	PM	aortic root procedures	344	189±68	245±92	-	**< 0.0001**	132±53	186 ±74	-	**< 0.0001**
Kuciński (2019)	DN vs BC	retro-spective	all cardiac procedures	2108	65 (50-85)	55 (42-72)	-	**< 0.001**	40 (29-59)	33 (24-47)	-	**< 0.001**
Luo (2019)	DN vs BC	PM	MI AVR/ MVR/DVR	132	98.00 (77.50-129.75)	105.50 (86.00-128.00)	-	0.428	56.50 (45.25-80.00)	61.50 (46.00-77.00)	-	0.368
Pragliola (2019)	DN vs BC	PM	all cardiac procedures	204	-	-	-	-	108±52	106±44	-	0.3
Sanetra (2019)	DN vs BC	RCT	AVR	150	67.96 ±20.46	69.25 ±19.23	-	0.564	55.18 ±15.93	55.52 ±14.03	-	0.419
Timek (2019)	DN vs BC	PM	CABG	650	85±26	99±28	-	**< 0.01**	68±20	82±24	-	**< 0.01**
Kim (2018)	DN vs BC	PM	valve procedures	208	99.1 ±39.4	155.2 ±62.4	-	**< 0.001**	75.3 ±31.7	102.1 ±47.3	-	**< 0.001**
Koeckert (2018)	DN vs BC	PM	MI AVR	118	77.6 ±27.3	74.8 ±16.5	-	0.492	58.1 ±17.7	56.6 ±11.8	-	0.591
Sabik (2018)	DN vs BC	PM	MI MVP	124	72.3 ±19.0	94.2 ±20.7	-	**< 0.0001**	51.3 ±15.7	66.4 ±16.8	-	**< 0.0001**
Ad (2017)	DN vs BC	RCT	CABG and/or single valve	89	97	103	-	0.288	70	83	-	0.018*
Hamad (2017)	DN vs BC	retro-spective	AVR + CABG	50	65.5 ±12.5	76.6 ±19.1	-	**0.019**	55.6 ±11.2	64.3 ±18.9	-	**0.05**
Ziazadeh (2017)	DN vs BC	PM	MI AVR	126	108±24	135±43	-	**Sign**	80±16		-	**Signifi-cant**
Kim (2016)	DN vs BC	PM	all cardiac procedures	78	158±68	162±58	-	0.786	97±42	101±41	-	0.662
Mischra (2016)	DN vs BC	retro-spective	CABG and DVR	100	158.60 ±39.92	179.81 ±42.36	-	**0.041**	110.15 ±36.84	133.56 ±35.66	-	**0.012**
Vistarini (2016)	DN vs BC	retro-spective	MI AVR	46	67±27	59±24	-	0.19	56±13	48±17	-	0.07
Ota (2015)	DN vs BC	PM	AVR	108	71±16	84±28	-	**0.003**	52±14	60±16	-	**0.004**
Rama-nathan (2015)	DN vs BC	retro-spective	all cardiac procedures	142	105.0	109.5	-	0.5862	71.3	72.0	-	0.9038
Sora-bella (2014)	DN vs BC	retro-spective	reoperative AVR	113	61.3 ±18.9	67.2 ±20.1	-	0.111	93.1 ±25.7	100.5 ±34.3	-	0.204
Duan (2021)	DN vs HTK	PM	complex valve surgery	146	149 (116 -181)	-	158 (126-187)	0.232	107 (74-134)	-	100 (83-133)	0.795
Gunaydin (2020)	DN vs HTK	RCT	MI AVR	200	-	-	-	-	99±27	-	102 ±33	0.7
Lee (2020)	DN vs HTK	PM	MICS	456	112.5 ±44.8	-	115.8 ±36.0	0.386	74.8 ±28.6	-	77.1	0.081
Mehra-banian (2018)	DN vs HTK	RCT	complex cardiac procedures	40	103.19 ±23.42	-	97.36 ±16.70	0.376	73.76 ±19.66	-		0.083

* Not significant due to alpha < 0.001

Table 4. Rate of electric defibrillation

Article	Year	Cardioplegia	Study design	Cardiac procedures	No. of patients	Defibrillation %			p value
						DN	BC	HTK	
Eris (2021)	2021	DN vs BC	retrospective	aortic root procedures	118	44.4	69.2	-	**0.006**
Lama (2021)	2021	DN vs BC	RCT	CABG	90	15.55	24.44	-	0.42
Ross (2021)	2021	DN vs BC	retrospective	all cardiac procedures	497	8	23	-	**< 0.001**
Sevuk (2021)	2021	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	10.2	15.9	-	0.26
Chen (2020)	2020	DN vs BC	PM	acute aortic dissection	122	11.3	46.7	-	**< 0.001**
Kirisci (2020)	2020	DN vs BC	RCT	CABG	60	10.00	6.67	-	0.64
Kuserli (2020)	2020	DN vs BC	PM	aortic root procedures	72	22.2	52.8	-	**0.007**
Sharma (2020)	2020	DN vs BC	retrospective	AVR + MVR	209	21.2	65.9	-	**0.00001**
Ad (2017)	2017	DN vs BC	RCT	CABG and/or single valve	89	4.7	13.2	-	0.244
Hamad (2017)	2017	DN vs BC	retrospective	AVR + CABG	50	20	60	-	**0.009**
Mischra (2016)	2016	DN vs BC	retrospective	CABG and DVR	100	4	4	-	1.000

Cardiac enzymes

In the majority of analyzed articles, the postoperative levels of cardiac enzymes (creatine phosphokinase myocardial band (CK-MB), troponin T or I (TnT and TnI), depending on study protocol) were similar or lower when DNC was compared with CBC cases (Table 3; download here). Different results were shown in the subgroup analysis of aortic root cases [2] with XC time > 180 min where CK-MB levels were significantly higher in the DNC group. Significantly higher postoperative TnT levels in the DNC group were reported also in a retrospective study of 2108 cardiac cases of all types [10]. However, a more thorough analysis revealed that uneven distribution of surgery types (resulting in longer CPB and XC times in DNC) and preoperative TnT level was responsible for that result. In two studies comparing DNC with HTK cardiac enzymes were comparable [22-23] between the groups.

Two other studies on DNC vs. HTK suggested a higher level of cardiac enzymes in cases when DNC was used with longer XC. Lee et al. [24] showed lower peak TnI and CK-MB in DNC. A peak level of cardiac enzymes according to the XC time was also lower in DNC, but the differences between groups tended to decrease with a crossover point of ~100 minutes of XC. In a sub-analysis of cases with a second cardioplegia dose, Gunaydin et al. showed significant differences in TnT levels measured during weaning from CPB to the disadvantage of DNC [25].

Cardiac activity and return to sinus rhythm

The quality of myocardial protection may be also estimated by observing the electrical and mechanical activity of the arrested heart: satisfactory protection is shown by no such activity before the clamp removal and reperfusion. Ucak et al. [8] reported ventricular fibrillation (VF) during XC in 5.7% of cases in DNC and 9.4% in the CBC group ($p = 0.016$). In the RCT by Sanetra et al. [26] no differences between groups in terms of electrical activity during XC were observed. In majority of the studies, patients with DNC more often had a spontaneous return of sinus rhythm (SR) return and less often needed electric defibrillation, compared to those with CBC (Table 4). When compared with HTK, only one study [23] reported a rate of spontaneous SR return. It was significantly higher in the DNC group and even more pronounced in a subgroup of cases with XC > 120 min (93.1% vs 42.3%). A very high number of VF in the HTK groups raises some questions.

Cardioplegia volume and blood product transfusion rates

In the majority of reviewed studies, total cardioplegia volume was significantly higher in the CBC than in the DNC cases [1, 4-6, 8-9, 11, 15, 17-18, 20, 26-33]. In only one study this volume was lower in CBC patients [21]. When only crystalloid volume is taken into consideration, higher volume was administered to patients who received DNC [1, 14, 31, 34-35]. The differences in administered volume did not seem to affect the postoperative hematocrit (HCT) levels. This parameter was analyzed in 10 articles and 6 of them reported comparable HCT levels between DNC and CBC [9, 11, 27-28, 31, 34]. In the other four studies, HCT was higher in the DNC group [6, 14, 18, 36].

The amount of transfused blood and blood products was similar in the majority of studies comparing DNC and CBC. Due to the lack of homogeneity in reporting between articles in Table 5, we present only data about red blood cell (RBC) transfusions. Three studies [6, 18, 34] showed a higher need for different kinds of blood products in the CBC group. When DNC was compared with HTK, haemoglobin levels as well as the rate of transfusions during CPB and in the postoperative period were comparable between the groups [22, 24-25]. Only Duan et al. [23] reported a higher need for platelet concentrates (PC), fresh frozen plasma and cryoprecipitate in the HTK group. In the subgroup analysis of cases with XC > 120 minutes, only differences in PC remain significant.

Table 5. RBC transfusions

Article	Cardioplegia	Study design	Cardiac procedures	No. of patients	RBC transfusions			p value
					DN	BC	HTK	
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	22%	26%	-	0.65
Reidy (2021)	DN vs BC	retrospective	CABG in veterans	155	25.7%	17.6%	-	0.41
Ross (2021)	DN vs BC	retrospective	all cardiac procedures	497	37%	35%	-	0.61
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	0.5 (0.0-1.0) U	1.0 (0.0-1.0) U	-	0.72
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	0.47±0.74 U	1.75±0.97 U	-	**0.001**
Orak (2020)	DN vs BC	retrospective	elective all cardiac procedures	83	76.6%	75.7%	-	0.87
Schutz (2020)	DN vs BC	PM	CABG or CABG and valve	670	1.97 U	1.67 U	-	0.45
Sanetra (2019)	DN vs BC	RCT	AVR	150	24.0%	29.3%	-	0.56
Koeckert (2018)	DN vs BC	PM	MI AVR	118	0.81±2.41 U	0.46±1.24 U	-	ns
Ad (2017)	DN vs BC	RCT	CABG and/or single valve	89	4%	7%	-	**0.658**
Hamad (2017)	DN vs BC	retrospective	AVR + CABG	50	0.68±0.95 U	1.32±1.89 U	-	0.136
Ziazadeh (2017)	DN vs BC	PM	MI AVR	126	0.24±0.80 U	0.24±0.56 U	-	ns
Vistarini (2016)	DN vs BC	retrospective	MI AVR	46	4%	48%	-	**0.006**
Sorabella (2014)	DN vs BC	retrospective	reoperative AVR	113	1.4±1.7 U	2.1±2.6 U	-	0.07
Duan (2021)	DN vs HTK	PM	complex valve surgery	146	0.75 (0.00-4.00) U	-	0.00 (0.00-4.00) U	0.682
Gunaydin (2020)	DN vs HTK	RCT	MI AVR	200	1.0±0.5 U	1.0±0.5 U	-	0.8
Lee (2020)	DN vs HTK	PM	MICS	456	893±1290 mL	-	907±1228 mL	0.905
Mehrabanian (2018)	DN vs HTK	RCT	complex cardiac procedures	40	38.1%	-	42.1%	0.525

Table 6. Postoperative AF occurrence

Article	Cardioplegia	Study design	Cardiac procedures	No. of patients	Atrial fibrillation [%]			p value
					DN	BC	HTK	
Eris (2021)	DN vs BC	retrospective	aortic root procedures	118	11.1	12.3	-	0.84
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	27	18	-	0.27
Reidy (2021)	DN vs BC	retrospective	CABG in veterans	155	30.0	24.7	-	0.46
Sanri (2021)	DN vs BC	retrospective	CABG	255	24.2	35.8	-	**0.044**
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time >90 min	176	21.6	29.5	-	0.22
Shu (2021)	DN vs BC	PM	all cardiac procedures	326	20.86	22.70	-	0.788
Algarni (2020)	DN vs BC	retrospective	all cardiac procedures	305	14.7	17.6	-	0.56
George (2020)	DN vs BC	PM	CABG or valve	286	7.7	6.3	-	0.643
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	22.2	25.0	-	0.781
Orak (2020)	DN vs BC	retrospective	elective all cardiac procedures	83	20.9	17.5	-	0.692
Schutz (2020)	DN vs BC	PM	CABG or CABG and valve	670	22.7	31.0	-	**0.018**
Ucak (2020)	DN vs BC	retrospective	AVR	137	28	24	-	0.71
Willekes (2020)	DN vs BC	PM	aortic root procedures	344	31.4	36.0	-	
Sanetra (2019)	DN vs BC	RCT	AVR	150	24	21	-	0.71
Timek (2019)	DN vs BC	PM	CABG	650	33	23	-	**< 0.01**
Koeckert (2018)	DN vs BC	PM	MI AVR	118	37.3	27.1	-	0.162
Sabik (2018)	DN vs BC	PM	MI MVP	124	18	28	-	0.18
Hamad (2017)	DN vs BC	retrospective	AVR + CABG	50	44	36	-	0.773
Ziazadeh (2017)	DN vs BC	PM	MI AVR	126	33	22	-	ns
Kim (2016)	DN vs BC	PM	all cardiac procedures	78	35.9	30.8	-	0.804
Mischra (2016)	DN vs BC	retrospective	CABG and DVR	100	30.00	16.67	-	0.22
Ota (2015)	DN vs BC	PM	AVR	108	37.0	33.3	-	0.84
Ramanathan (2015)	DN vs BC	retrospective	all cardiac procedures	142	31	31	-	ns
Gunaydin (2020)	DN vs HTK	RCT	MI AVR	200	18.9	-	11.5	**0.035**

Heart rhythm disturbances in the postoperative period

The majority of reviewed articles showed comparable results between DNC and CBC in terms of postoperative atrial fibrillation (AF) occurrence (Table 6). Only Timek et al. [11] reported a higher rate of AF after isolated CABG with DNC. Opposite results with a higher rate of AF in CBC cases were shown in the two studies. The first of which [20] showed a correlation between the occurrence of AF and cardioplegia volume in patients who underwent isolated CABG. In the second study, [37] patients who underwent CABG with or without valve intervention had a higher rate of AF, atrial flutter and VT in cases with CBC in all analyses excluding subgroups with left ventricular ejection fraction (LVEF) < 35%.

Shu et al demonstrated a comparable rate of AF but higher risk of ventricular rhythm disturbances was shown in PSM analysis as well as in sub-analysis of cases with XC > 69 minutes [38]. In log regression analysis DNC had a significant effect on reduction in the rate of ventricular arrhythmias.

The need for a temporary pacemaker was equal [39] or higher in DNC groups [40] when compared with CBC.

Two studies comparing DNC with HTK presented results on postoperative arrhythmia. Gunaydin et al. [25] reported a higher rate of AF and atrioventricular (AV) block in the general cohort and subgroup with a second cardioplegia dose when DNC was used. When only one dose was administered, the results were comparable. Different results were reported by Duan et al. [23]. 3rd degree AV block, VF and sudden cardiac arrest were more frequent in the HTK group. However, in the logistic regression model, the type of cardioplegia did not have a statistically significant influence on the occurrence of severe post-operative arrhythmia. No differences were found in a sub-analysis of cases with XC > 120 minutes.

Inotropic/vasoactive support and low cardiac output syndrome

Due to heterogeneity in reporting it is difficult to show and analyze differences in the need for inotropic/vasopressor support. Only Orak et al. [27] report lower noradrenaline (NA) requirements during surgery when CBC was used. Seven of reviewed articles showed a lower need for inotropic/vasopressor support in the DNC group [2, 4, 7-8, 11, 15, 18]. In Ad et al. [31] the need for inotropic support was also lower in the DNC group, but significance was not reached due to an alpha level of $p < 0.001$. A total of 19 other articles reported no differences in terms of the need for inotropic/vasoactive and rate of low cardiac output syndrome (LCOS) between DNC and CBC. Three [22, 24-25] of a total of four studies comparing DNC and HTK showed no differences in the need for inotropic support. Only in one sub-analysis of cases with XC < 120 minutes from the study by Duan et al. [23] the doses of NA were lower in the DNC group.

Non-cardiac or systemic complications

Ross et al. [30] showed no differences in the rate of acute kidney injury (AKI), stroke or composite death. However, the

Table 7. Early mortality

Article	Cardio-plegia	Study design	Cardiac procedures	No. of patients	RBC transfusions			p value	info
					DN	BC	HTK		
Eris (2021)	DN vs BC	retro-spective	aortic root procedures	118	3.7	3.0	–	0.851	30 days
Kagan (2021)	DN vs BC	retro-spective	CABG	350	3.8	4.6	–	0.898	in-hospital
Lama (2021)	DN vs BC	RCT	CABG	90	0	2.2	–	1.000	in-hospital
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	3.6	0	–	0.15	30 days or in-hospital
Reidy (2021)	DN vs BC	retro-spective	CABG in veterans	155	0	2.4	–	0.5	30 days
Ross (2021)	DN vs BC	retro-spective	all cardiac procedures	497	1	2	–	0.43	in-hospital
Sanri (2021)	DN vs BC	retro-spective	CABG	255	5.3	5.7	–	0.892	30 days
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	2.3	3.4	–	1.000	in-hospital
Algarni (2020)	DN vs BC	retro-spective	all cardiac procedures	305	0.4	1.4	–	0.43	in-hospital
Chen (2020)	DN vs BC	PM	acute aortic dissection	122	4.83	6.67	–	0.964	in-hospital
George (2020)	DN vs BC	PM	CABG or valve	286	0	0	–	–	30 days
Kirisci (2020)	DN vs BC	RCT	CABG	60	6.67	3.33	–	0.55	in-hospital
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	2.8	2.8	–	1.000	in-hospital
Schutz (2020)	DN vs BC	PM	CABG or CABG and valve	670	1.8	2.1	–	0.758	operative mortality
Shi (2020)	DN vs HTK	PM	aortic root procedures	86	0	0	–	–	in-hospital

Table 7. continuation

Article	Cardio-plegia	Study design	Cardiac procedures	No. of pa-tients	RBC transfusions			p value	info
					DN	BC	HTK		
Ucak (2020)	DN vs HTK	retro-spective	AVR	137	0	1.2	–	0.512	30 days
Willekes (2020)	DN vs HTK	PM	aortic root procedures	344	5.2	4.7	–	0.8035	30 days
Kuciński (2019)	DN vs BC	retro-spective	all cardiac procedures	2108	3.6	3.0	-	0.54	in-hospital
Luo (2019)	DN vs HTK	PM	MI AVR/ MVR/DVR	132	1.52	1.52	–	1.000	in-hospital
Pragliola (2019)	DN vs BC	PM	all cardiac procedures	204	3.9	3.9	–	1.000	in-hospital
Sanetra (2019)	DN vs BC	RCT	AVR	150	1.3	0	–	1.000	30 days
Timek (2019)	DN vs BC	PM	CABG	650	1.5	1.2	–	1.000	30 days
Kim (2018)	DN vs HTK	PM	valve procedures	208	0	1.9	–	> 0.99	30 days or in-ho-spital
Koeckert (2018)	DN vs HTK	PM	MI AVR	118	0	0	–	–	30 days
Willekes (2020)	DN vs HTK	retro-spective	all cardiac procedures	2108	3.6	3.0	-	0.54	in-hospital
Kuciński (2019)	DN vs HTK	retro-spective	all cardiac procedures	2108	3.6	3.0	-	0.54	in-hospital
Luo (2019)	DN vs BC	PM	MI AVR/ MVR/DVR	132	1.52	1.52	-	1.000	in-hospital
Pragliola (2019)	DN vs BC	PM	all cardiac procedures	204	3.9	3.9	-	1.000	in-hospital
Sanetra (2019)	DN vs BC	RCT	AVR	150	1.3	0	-	1.000	30 days
Timek (2019)	DN vs BC	PM	CABG	650	1.5	1.2	-	1.000	30 days
Kim (2018)	DN vs BC	PM	valve procedures	208	0	1.9	-	> 0.99	30 days or in-hospital
Koeckert (2018)	DN vs BC	PM	MI AVR	118	0	0	-	-	30 days
Sabik (2018)	DN vs BC	PM	MI MVP	124	0	0	-	-	in-hospital
Ad (2017)	DN vs BC	RCT	CABG and/or single valve	89	0	0	-	-	operative mortality
Hamad (2017)	DN vs BC	retro-spective	AVR + CABG	50	0	4	-	1.000	in-hospital
Ziazadeh (2017)	DN vs BC	PM	MI AVR	126	0	3.1	-	ns	30 days
Kim (2016)	DN vs BC	PM	all cardiac procedures	78	2.6	0	-	-	operative mortality
Mischra (2016)	DN vs BC	retro-spective	CABG and DVR	100	0	2	-	0.314	in-hospital

Table 7. continuation

Article	Cardio-plegia	Study design	Cardiac procedures	No. of pa-tients	RBC transfusions			p value	info
					DN	BC	HTK		
Vistarini (2016)	DN vs BC	retro-spective	MI AVR	46	0	0	-	> 0.99	in-hospital
Ota (2015)	DN vs BC	PM	AVR	108	0	0	-	-	in-hospital
Rama-nathan (2015)	DN vs BC	retro-spective	all cardiac procedures	142	7.0	1.4	-	ns	in-hospital
Sorabella (2014)	DN vs BC	retro-spective	reoperative AVR	113	0	1.6	-	1.000	in-hospital
Duan (2021)	DN vs HTK	PM	complex valve surgery	146	4.1	-	8.2	0.302	30 days
Gu-naydin (2020)	DN vs HTK	RCT	MI AVR	200	2.10	-	1.04	0.7	in-hospital
Lee (2020)	DN vs HTK	PM	MICS	456	0.4	-	0.4	> 0.99	30 days or during index hospitali-zation

risk of reoperation caused by bleeding was higher in the DNC group. In the sub-analysis of CABG cases the post-operative levels of creatinine were significantly lower in the DNC group but so were the pre-operative levels. A RCT by Santera et al. [26] reported that the rate of significant creatinine increase (> 25% or > 0.5mg/dL) or AKI was greater in the CBC group. The retrospective study by Eris et al. [18] also showed that AKI was more frequent in the CBC group. Further analysis revealed it only applies to the AKI Stage 1. There were no differences in the rate of other complications (cerebrovascular incident, infection, AF, bleeding, respiratory failure) or mortality. Stage 1 AKI (or any AKI) in CBC was also more frequent in a retrospective study by Kagan et al. [21] In logistic regression analysis AKI was correlated, among others, with increased cardioplegia volume.

Luo et al. [33] showed significantly lower levels of blood urea nitrogen (BUN) in the DNC group, without differences in the post-operative levels of creatinine, eGFR or pre-operative BUN. However, the DNC group had a significantly lower Euro SCORE II. Schutz et al. [37] reported a significantly higher rate of neurological complications in the postoperative period in DNC for the overall cohort (CABG + valve procedure), as well as for the subgroup with LVEF < 35%. The rate of stroke was also significantly higher in this subgroup when DNC was used. The frequency of total infections and total sternal infections was greater in the CBC group for the overall cohort. Overall, most studies did not reveal differences in the rate of postoperative complications between groups. It is noteworthy that almost all of the reviewed articles analyzed different kinds of complications with different definitions. Early mortality was the complication that was most often studied (in 37 studies, see Table 7) [1-6, 8-21, 23-26, 28-35, 37, 39-42].

Echocardiographic findings

Only George et al. [39] reported significantly lower LVEF measured on the 5th post-operative day (POD) in the DNC group, although the median values in both groups were in the normal range.

Four [1, 6, 16, 36] studies (including one RCT), all describing different types of cardiac surgeries, showed better echocardiographic parameters in the DNC group measured at different time points during hospitalization. No differences were shown in other studies comparing DNC and CBC (Table 8).

Two RCTs on DNC versus HTK [22, 25] reported no differences in the LVEF measured before discharge. In the study by Mehrebenian et al. [22], LVEF measured in the OR after weaning from CPB was also comparable. In Duan et al. [23] LVEF measured in the postoperative period was also similar between groups, however systolic volume and cardiac output (as echocardiographic parameters) were significantly lower in HTK, both in the general cohort and subgroup of XC ≥ 120 minutes. Whereas the sub-analysis of cases with XC < 120 minutes showed no differences. [23]

Length of ICU and hospital stay, mechanical ventilation time

The majority of articles presented comparable hospital and intensive care unit (ICU) length of stay (LOS) (Table 9) and time of mechanical ventilation between the DNC and CBC cases. A shorter ICU stay for the DNC group was reported in 2 studies [4, 38], with patients undergoing all types of cardiac procedures. In their study concerning AVR reoperations, Sorabella et al. [29] reported no differences in the ICU LOS and mechanical ventilation time, although hospital LOS was significantly shorter when DNC was used. Similar results

Table 8. LVEF

Article	Cardio-plegia	Study design	Cardiac procedures	No. of patients	postoperative LVEF [%]			p value	Time point
					DN	BC	HTK		
Eris (2021)	DN vs BC	retro-spective	aortic root procedures	118	50.3±7.5	49.7±8.2	-	0.714	before discharge
Lama (2021)	DN vs BC	RCT	CABG	90	56.33±8.94	50.45±8.55	-	**< 0.001**	before discharge
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	54±1	55±1	-	0.3	before discharge
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	55(45-55)	50(45-55)	-	0.08	before discharge
Shu (2021)	DN vs BC	PM	all cardiac procedures	326	60.0 (50.5-62.0)	59.0 (48.5-61.0)	-	0.263	within 48h post-op
George (2020)	DN vs BC	PM	CABG or valve	286	53.4 (45.1-57.1)	56.0 (51.7-57.6)	-	**< 0.001**	5th post--op day
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	53.75±6.14	50.00±5.07	-	**0.006**	before discharge
Shi (2020)	DN vs BC	PM	aortic root procedures	86	60.07±9.57	58.37±8.83	-	0.395	post-op
Ucak (2020)	DN vs BC	retro-spective	AVR	137	56.70±5.30	55.42±4.90	-	0.508	routine post-op
Pragliola (2019)	DN vs BC	PM	all cardiac procedures	204	46±10	47±9	-	0.5	before discharge
Sanetra (2019)	DN vs BC	RCT	AVR	150	54.64±6.49	54.61±5.63	-	0.708	2-3 days post-op
Timek (2019)	DN vs BC	PM	CABG	650	53±13	54±12	-	0.36	follow-up
Sabik (2018)	DN vs BC	PM	MI MVP	124	56.70±6.92	54.20±8.72	-	0.077	on discharge
Hamad (2017)	DN vs BC	retro-spective	AVR + CABG	50	59.4±8.3	58.1±8.9	-	0.601	post-op
Vistarini (2016)	DN vs BC	retro-spective	MI AVR	46	61.5±6.0	59.1±3.8	-	0.15	on di-scharge
Sorabella (2014)	DN vs BC	retro-spective	reoperative AVR	113	48.5±10.7	46.8±10.9	-	0.401	post-op
Duan (2021)	DN vs HTK	PM	complex valve surgery	146	57(49-62)	-	54(45-62)	0.261	"periopera-tive"
Gunaydin (2020)	DN vs HTK	RCT	MI AVR	200	41.0±10.0	-	42.5±10.0	0.6	before discharge
Mehra-banian (2018)	DN vs HTK	RCT	complex cardiac procedures	40	41.67±12.32	-	41.79±7.15	0.97	on di-scharge

Table 9. Hospital and ICU LOS

Article	Cardioplegia	Study design	Cardiac procedures	No. of patients	ICU LOS [d] or [h]			p value	Hospital LOS [d]			p value
					DN	BC	HTK		DN	BC	HTK	
Eris (2021)	DN vs BC	retro-spective	aortic root procedures	118	2.3 ±0.6 [d]	2.4 ±0.9 [d]	-	0.165	7.6±1.4	7.8 ±2.2	-	0.489
Kagan (2021)	DN vs BC	retro-spective	CABG	350	2.94± 3.20 [d]	2.90± 3.30	-	0.494	7.34 ±3.12	7.70 ±4.14	-	**< 0.001**
Lama (2021)	DN vs BC	RCT	CABG	90	3.47 ±1.09 [d]	3.49± 1.75 [d]	-	0.35	6.07 ±1.34	6.64 ±2.81	-	0.21
Lenoir (2021)	DN vs BC	PM	aortic root procedures	110	1.80± 0.20 [d]	1.60± 0.15 [d]	-	0.32	5.5±0.3	5.6±0.3	-	0.27
Reidy (2021)	DN vs BC	retro-spective	CABG in veterans	155	3.9 (2.9-5.9) [d]	3.5 (2.1-5) [d]	-	0.16	7.4 (6.1-13.2)	7.2 (6-11.1)	-	0.28
Ross (2021)	DN vs BC	retro-spective	all cardiac procedures	497	47 (25-91) [h]	47 (26-114) [h]	-	0.27	8 (6-12)	7 (6-10)	-	0.87
Sanri (2021)	DN vs BC	retro-spective	CABG	255	3.06± 3.90 [d]	3.08± 3.31 [d]	-	0.52	6.89 ±3.27	7.23± 2.56	-	**< 0.001**
Sevuk (2021)	DN vs BC	PM	all cardiac procedures and XC time > 90 min	176	1 (1-2) [d]	1 (1-2) [d]	-	0.09	5 (5-6)	5 (5-6)	-	0.24
Shu (2021)	DN vs BC	PM	all cardiac procedures	326	1.97± 1.58 [d]	2.55± 2.36 [d]	-	0.0103	-	-	-	-
Algarni (2020)	DN vs BC	retro-spective	all cardiac procedures	305	3 (2-5) [d]	4 (2-6) [d]	-	0.047	9 (7-14)	11 (7-19)	-	0.1
Chen (2020)	DN vs BC	PM	acute aortic dissection	122	7.9± 2.1 [d]	8.1 ±2.3 [d]	-	0.617	-	-	-	-
George (2020)	DN vs BC	PM	CABG or valve	286	3.1±0.8 [d]	3.1±0.5 [d]	-	0.931	7 (6-8)	7 (6-9)	-	ns
Kirisci (2020)	DN vs BC	RCT	CABG	60	2.23± 0.68 [d]	2.23± 0.43 [d]	-	1.000	7.11 ±0.63	7.00 ±0.64	-	0.52
Kuserli (2020)	DN vs BC	PM	aortic root procedures	72	2 (2-5) [d]	3 (2-6) [d]	-	0.681	-	-	-	-
Sharma (2020)	DN vs BC	retro-spective	AVR + MVR	209	2.10± 0.34 [d]	2.10± 0.30 [d]	-	0.447	5.90 ±0.90	5.98 ±0.90	-	0.52
Shi (2020)	DN vs BC	PM	aortic root procedures	86	52.19 ±75.10 [h]	34.74 ±27.41 [h]	-	0.156	8.88 ±3.93	8.93 ±3.63	-	0.955
Ucak (2020)	DN vs BC	retro-spective	AVR	137	29.6 ±5.1 [h]	28.4 ±6.6[h]	-	0.685	6.2±2.8	6.2±2.4	-	0.795
Koeckert (2018)	DN vs BC	PM	MI AVR	118	43.1± 57.8 [h]	29.3± 23.9 [h]	-	0.098	6.7±4.5	5.4±2.3	-	0.116
Hamad (2017)	DN vs BC	retro-spective	AVR + CABG	50	59.4± 42.8 [h]	44.3± 41.0 [h]	-	0.213	6.8±2.5	8.7±5.4	-	0.127
Ziazadeh (2017)	DN vs BC	PM	MI AVR	126	33±43[h]	34±50 [h]	-	ns	5.8±2.5	5.9±2.7	-	ns
Vistarini (2016)	DN vs BC	retro-spective	MI AVR	46	51.7 ±52.9 [h]	51.6 ±50.4 [h]	-	> 0.99	7.9±3.8	7.1±2.3	-	0.38
Ota (2015)	DN vs BC	PM	AVR	108	2.6 ±2.1 [d]	3.7 ±3.9 [d]	-	0.079	8.3 ±10.6	8.8±8.1	-	0.816
Rama-nathan (2015)	DN vs BC	retro-spective	all cardiac procedures	142	-	-	-	-	14.0	16.2	-	0.3135

Table 9. continuation

Article	Cardioplegia	Study design	Cardiac procedures	No. of patients	ICU LOS [d] or [h]			p value	Hospital LOS [d]			p value
					DN	BC	HTK		DN	BC	HTK	
Sorabella (2014)	DN vs BC	retrospective	reoperative AVR	113	2.8 ±2.0 [d]	4.1±7.0 [d]	-	0.193	7.9±3.4	10.1 ±7.2	-	**0.035**
Duan (2021)	DN vs HTK	PM	complex valve surgery	146	29 (20-68) [h]	-	43 (21-75) [h]	**0.024**	8 (7-11)	-	9 (7-11)	0.933
Gunaydin (2020)	DN vs HTK	RCT	MI AVR	200	1.8 (0.5-3.6) [d]	-	1.0 (0.4-1.7) [d]	0.41	6.4 (4.5-8.4)	-	5.6 (4.9-7.1)	0.56
Lee (2020)	DN vs HTK	PM	MICS	456	1 (1-2) [d]	-	1 (1-2) [d]	0.468	7 (6-10)	-	7 (6-9)	0.126
Mehrabanian (2018)	DN vs HTK	RCT	complex cardiac procedures	40	2.22 ±0.45 [d]	-	2.53 ±0.68 [d]	0.101	-	-	-	-

can be found in two retrospective studies on isolated CABG [20-21]. Significantly shorter mechanical ventilation time in the CBC group was reported by Vistarini et al. [34]. In a sub-analysis of cases with longer XC time requiring a second DNC or HTK dose, Gunaydin et al. [25] reported significantly longer ICU LOS and hospital LOS in the DNC group. No differences were shown when only one dose of either DNC or HTK was used. Mechanical ventilation time was comparable in all analyses. Duan et al. [23] observed that the ICU LOS was significantly shorter in the DNC group, both in the general cohort after PSM and in the sub-analysis of cases with XC < 120 minutes. In XC ≥ 120 minutes cases ICU LOS was comparable between groups. None of the sub-analyses in that study revealed differences in the hospital LOS.

Discussion

All of the currently used cardioplegic solutions are safe and well-designed. The oldest of them, high-potassium CBC, is also the most widely used in the world [43]. CBC has great buffering properties and ensures cardiac arrest in a highly oxygenated environment. Its oncotic properties prevent cell oedema and its twenty minutes re-dosing period provides re-oxygenation and washout of waste products, which improves the preservation of ATP [39]. DNC developed by the team from Boston Children's Hospital [44] is also a high-potassium solution. The main purpose of its chemical composition was to ensure the lowest possible intracellular accumulation of calcium, which is particularly elevated in depolarizing cardiac arrest. Depolarization creates higher sodium and calcium gradient, which leads to cell calcium overload – the main factor of IRI. Calcium influx is one of the mechanisms leading to mitochondrial dysfunction and reperfusion fibrillation [23].

High potassium levels may also lead to vasoconstriction and disrupt the endothelium function in coronary and peripheral vessels aggravating the damage during reperfusion [45]. DNC contains lidocaine (a Na^+-K^+ pump blocker) which counteracts the unfavourable effects of depolarization by stabilizing the cell membrane, lowering excitability and elongating the refraction period [46]. All these actions reduce the probability of hypercontraction due to high Ca^{2+} concentration. What is more DNC itself contains a small amount of Ca^{2+}. Additionally, lidocaine has a protective effect on the endothelium.

In some cardioplegia strategies, lidocaine can be administered into the peripheral circulation [31], however, it is more effective when injected directly into the coronary circulation. Unlike CBC, DNC has low nutritional value due to the small amount of blood and glucose. On the other hand, a small amount of blood leads to lower hematocrit (ca. 6-7%), which compared to CBC (ca. 26-32%) may provide better distribution in the coronary microcirculation. Such lower hematocrit could be beneficial, particularly in low temperatures when blood viscosity increases.

Better distribution means better cardioprotection and lower postoperative cardiac enzymes. HTK acts differently from the two above-mentioned solutions. A low-sodium solution causes membrane hyperpolarization, which leads to a reversible diastolic arrest. Better cell membrane stabilisation provides lower permeability for ions such as Ca^{2+}. An additive of Mg^{2+} in HTK also stabilizes cardiomyocyte cell membranes, yet lidocaine seems to be superior and more effective.

Quality of cardioprotection: cardiac enzymes

Cardiac enzymes are one of the most reliable markers of cardioprotection during the cardiac surgery procedure. Elevated postoperative Tn or CK-MB level correlates with early outcomes and mortality of cardiac surgery patients. The majority of analyzed studies showed equally good or better cardioprotection in DNC cases when correlated with cardiac enzyme levels. The weak point is again the heterogeneity of reporting. Study protocols differ in terms of the time point of collecting blood samples, the measurement's accuracy over time [47], application and degree of hypothermia, cardioplegia administration and redosing protocols.

Quality of cardioprotection: post cross-clamp ventricular fibrillation

An indirect sign of cardioprotection is the heart's electrical activity during the procedure. In two studies analyzing this parameter, DNC was more effective in lowering the electrical activity of the heart.

Spontaneous return of SR after cross-clamp removal also gives information about cardioprotection. Longer ischemia and lower quality of cardioprotection increase the probability of VF and the need for defibrillation. Once again, the reported values are not homogeneous but are enough to make some conclusions. What draws attention is a significantly higher percentage of spontaneous SR return in DNC groups in the vast majority of the analysed studies. This illustrates good cardioprotection and control of Ca^{2+} accumulation mechanisms in cardiomyocytes, which is a main factor of VF after XC [42].

Hypothermia prolongs repolarization and is a known pro-arrhythmic factor. Constant cooling of the myocardium during many CBC repetitions may trigger VF. Slow rewarming of the heart after only one dose of DNC could be a protective factor [26]. However, this effect is not visible in HTK (also a single-dose cardioplegia solution) and probably plays an additional role in cardioplegia composition.

Less VF after XC removal means less direct current shocks and less myocardial damage, which may lower the concentrations of post-operative cardiac enzymes. Discrepancies in the VF:SR ratio noted in the studies may be due to the differences in the cardioplegia administration protocols or the patient population.

Quality of cardioprotection: echocardiographic parameters

Decreased contractility in the post-operative period may be the result of poor cardioprotection. All but one study [39] showed similar or better cardiac function in echocardiographic examination in the DNC groups when compared with CBC or HTK. It is noteworthy that not all of the articles analyzed changes between pre- and post-operative examinations. Duan et al. [23] comparing DNC and HTK reported better post-operative systolic volume and cardiac output measured by echocardiography in the former. However, this ratio does not necessarily indicate better heart function, only an increase in extracellular fluid. There is no evidence that LV mass influences cardioprotection [12]. However, LV hypertrophy and the presence of coronary disease in adults may have a negative effect the quality of cardioprotection in comparison with the pediatric population. Hypertrophied myocardium has a metabolism similar to that of fetal myocardium (increased glycolysis, reduced oxidation of fatty acids), which leads to reduced ischemia tolerance. This may suggest a better effect of DNC developed for similar conditions.

Postoperative complications

There is no evidence that the use of DNC reduces the number of postoperative complications. A relatively small number of analyzed cases may cause problems with obtaining statistical significance of rare complications. Differences in reporting also make it difficult to draw clear conclusions, as in the case of vasoactive or inotropic agent administration. LCOS may be a consequence of inadequate cardioprotection requiring vasoactive/inotropic support or even mechanical circulatory support. Almost every study had a different method of reporting data, thus making it difficult to compare them. However, in general patients with DNC had a similar or even lower need for vasoactive and inotropic agents.

The possible indirect influence of DNC on renal function is noteworthy. In four studies the DNC patients had better renal parameters [26, 33] or less frequent occurrence of AKI [18, 21, 26]. In studies by Eris and Kagan, this only applied to stage 1 AKI [18, 21]. Sanetra et al. hypothesized that lidocaine as a vasodilator could improve renal flow which in addition to shorter CPB and better cardiac function in the postoperative period may have a positive effect on kidney function [26]. A trend towards better renal function is also seen in metanalysis by Misra et al. [48].

Questions and limitations of the review

Two main DNC dosing protocols can be found in the literature. The first method is a constant volume (usually 1000 or 1500 ml) delivered regardless of the patient's body weight. The second approach is dosing based on the patient's body weight (typically 20 mL/kg), with or without an indication of the maximum dose.

However, the method of administering the additional DNC doses remains unclear due to the lack of a standard dosing schedule. The most common rule is re-dosing ½ of the initial DNC dose after 60 minutes of XC if the expected total XC time is > 90 minutes. Many modifications to the re-dosing period or the volume and composition of the second DNC dose can be found in the literature [49-52]. The authors of the analyzed studies did not always include the protocols for administration and re-dosing of DNC. Those potential differences in dosing may be responsible for inconsistent results, particularly because the vast majority of the reviewed articles were retrospective.

Conclusions

The currently used cardioplegic solutions are safe and have proven properties to protect the heart against the effects of ischemia during open-heart surgery. The differences between DNC, CBC and HTK described in the analyzed studies do not disqualify any of the solutions but may suggest the need for further research, particularly in the context of longer XC times. More randomized trials are needed, possibly also examining cardiac function in a long-term follow-up.

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The authors do not have anyconflict of interest in this project.

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