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Original Article

Paediatrics Section

Short-term Effects of Cardiopulmonary Bypass Temperature on Intracardiac Repair for Tetralogy of Fallot: A Retrospective Single Centre Observational Study

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ABSTRACT

Introduction: Tetralogy of Fallot (TOF) is a common cyanotic disease and the concept of ideal Cardiopulmonary Bypass (CPB) temperature is still controversial.

Aim: To assess the merits and demerits in terms of short term patient outcome of normothermic CPB over hypothermic CPB during intracardiac repair of TOF amongst paediatric patients.

Materials and Methods: Among 71 patients of TOF who underwent Intracardiac Repair (ICR) in the Department of Cardiovascular and Thoracic Surgery from 1st January, 2016 to 30th April, 2017, 60 patients were included in our single centre retrospective observational study.

Normally distributed variables were expressed by their mean and standard deviation; non normally distributed variables were expressed by their medians and interquartile ranges; categorical variables were expressed as n (%). Statistical software Stata IC version 14, R version 3.2.1 and MedCal were used. All tests were two-tailed with level of significance as <0.05.

Results: Normothermic CPB resulted in reduced post-operative Intensive Care Unit (ICU) and hospital stay, lesser incidence of delayed extubation and post-operative Right Ventricular (RV) dysfunction and lesser transfusion requirements of Fresh Frozen Plasma (FFP). ($p<0.05$). There was no impact of the CPB temperature on renal function, mean blood sugar levels, coagulation parameter and post-operative drain output, post-operative fever, wound infection, arrhythmia or re-exploration.

Conclusion: ICR for TOF under normothermic CPB is feasible and results in better post-operative outcomes in terms of duration of ventilation, ICU and hospital stay and RV functions.

Keywords: Congenital heart disease, Hypothermia, Normothermia

INTRODUCTION

Since the first successful use of the heart lung machine by Dr John Gibbon in 1953, CPB has been an indispensable part of cardiac surgery [1]. However, it is still associated with some complications [2].

Cooling of the whole body has been an integral part of congenital cardiac surgery [3]. The main advantage of it is to reduce the metabolic rate, there by decreasing the chances of ischaemic injury to the vital organs. However, hypothermia is also associated with negative effects on the enzymatic functions and cellular integrity [2]. Normothermic CPB on the contrary provides distinct advantages in this regard [3]. But, there have been studies showing mixed results. Tumour necrosis factor was seen to increase significantly in normothermia in the study performed by Menasche P et al., [4]. Serum levels of interleukin (IL)-6, IL-8, tumour necrosis factor-(alpha), IL-1(beta), and Polymorphonuclear (PMN) elastase were measured before and after CPB by Ohata T et al., and they found similar levels associated with both normothermia and hypothermia [5]. Stocker CF et al., have demonstrated that CPB temperature has no effects on both systemic inflammatory response as well as organ injury [6].

TOF is the most common cyanotic heart disease world-wide [7]. The optimal surgical management of this condition has evolved over many years starting from two-stage to primary repairs to single stage repairs [8]. A transatrial/transpulmonary approach is the preferred technique of repair these days [9].

Latest and emerging research topics pertaining to TOF have been on: genetics, imaging and possible treatment modifications [10]. The ideal CPB perfusion temperature in congenital cardiac surgery is a topic full of controversies. While some studies have favoured normothermia, others have shown better outcomes associated with hypothermia [4-6]. Thus we had selected this topic which can not only lead to better management and outcomes of TOF in future, but also throw more light in terms of solving the controversies regarding the CPB temperatures. Similar study on the effect of CPB temperature on a single type of cardiac surgery has not yet been done, and thus we hope that by taking away the confounding factors of the cardiac disease and the type of surgery, the impact of CPB temperature will be reflected better by the outcome.

MATERIALS AND METHODS

Among 71 patients of TOF who underwent ICR in the Department of Cardiovascular and Thoracic Surgery from 1st January, 2016 to 30th April, 2017, six had previous modified BT shunts, three required deep hypothermic circulatory arrest, two got self-extubated post-operatively. These 11 patients were excluded and the remaining 60 patients were finally included for retrospective analysis of results. The total number of cases included in the study was based on the number of patients available who had undergone the above mentioned surgical procedure at our institute over the period of time mentioned. Informed consents were taken from the parents to allow the results of analysis being published.

All procedures performed in the cases were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was taken from the Institutional Ethics Committee (Letter number: CTVS/15-331).

Inclusion Criteria

Patients below 18 years of age, who underwent ICR for TOF and whose parents had given informed consent, were included.

Exclusion Criteria

Patients with prior cardiac/thoracic surgery, TOF with other major intracardiac anomalies, those requiring deep hypothermic circulatory arrest, patients with significant comorbidities and syndromic patients, emergency cases and patients unwilling to participate were excluded.

A retrospective analysis of outcome of CPB temperature was done. Thirty patients who had undergone normothermic CPB and 30 patients who had undergone hypothermic CPB were divided into two groups and results were analysed between them.

Assessment of Outcomes

Objective data were obtained from the patients' medical records.

Primary Outcomes

In this study, the co-primary endpoints were requirement of inotropic support, total duration of post-operative mechanical ventilation, total duration of post-operative hospital stay.

Secondary Outcomes

The secondary outcomes were in-hospital mortality and morbidity rates in each group.

Morbidity was defined as prolonged intubation (greater than six hours post-operatively), need for re-exploration, post-operative wound infection, need for re-intubation during the first 24 hours from extubation (failure of extubation), post-operative fever, prolonged post-operative ICU stay (more than seven days), post-operative renal dysfunction (>30% decrease in serum creatinine clearance levels in the post-operative period as compared to preoperative baseline values).

Other secondary outcomes were intraoperative need for vasodilators/vasoconstrictors, after coming off CPB need for DC (direct current) shock to revert to normal sinus rhythm, after coming of CPB following adequate rewarming presence of cardiac arrhythmias, post-operative blood loss, transfusion requirements, biventricular function (from echocardiography), blood gas parameters, blood sugar levels, clotting parameters, haemolysis (recorded in terms of presence or absence of it in terms of urine colour) and total post-operative duration of ICU stay.

STATISTICAL ANALYSIS

Normally distributed variables were expressed by their mean and standard deviation; not normally distributed variables were expressed by their medians and interquartile ranges; categorical variables were expressed as n(%). In test groups of continuous normally distributed variables, Student's t-test was used. Likewise if continuous data were not normally distributed the Mann-Whitney U test was used. Categorical were compared with the Chi-square test or Fisher's-exact tests (if expected cell count <5) between two study groups or when appropriate as relative risks. Statistical uncertainty was expressed by 95% confidence levels. Baseline balance was statistically tested.

Time to event variables were analysed using univariate nonparametric Kaplan Meier survival analysis and a Cox proportional hazard model adjusted for possible imbalances of patients' baseline characteristics. Time course variables were analysed using repeated measure ANOVA (analysis of variance) and a linear mixed model. Area under curve for various blood parameters were also estimated and compared between two trial arms. Statistical softwares Stata IC version 14, R version 3.2.1 and MedCal were used for analysis and all tests were two-tailed with level of significance as <0.05.

RESULTS

In the normothermia group out of the 30 patients, 13 (43.3%) were females and 17 (56.7%) were males. In the hypothermia group 14 (46.7%) were females and 16 (53.3%) were males.

The two groups were comparable in terms of the age, height, weight and Body Surface Area (BSA), Myocardial Performance Index (MPI) Right Ventricle and Left Ventricle (RV and LV), as well as presence or absence of Major Aortopulmonary Collaterals MAPCAs) [Table/Fig-1,2].

Preoperative	Groups	Mean	Std. Deviation	p-value
HB (g/dL)	Normothermia	16.583	3.7326	0.78
	Hypothermia	18.327	3.8062	
TLC (/cumm)	Normothermia	10243.33	3105.355	0.30
	Hypothermia	9433.33	3004.632	
Platelets (X 1000/cumm)	Normothermia	228.87	88.142	0.35
	Hypothermia	205.43	107.036	
Urea (mg/dL)	Normothermia	23.49	7.238	0.19
	Hypothermia	26.12	8.400	
Creatinine clearance (mL/min)	Normothermia	70.687	33.3822	0.80
	Hypothermia	73.240	44.7003	
Bilirubin (mg/dL)	Normothermia	0.683	0.4274	0.46
	Hypothermia	0.610	0.2190	
INR	Normothermia	1.1123	0.08728	0.24
	Hypothermia	1.1417	0.10619	
MPI (LV)	Normothermia	0.3550	0.02862	0.895
	Hypothermia	0.3560	0.02978	
MPI (RV)	Normothermia	0.3180	0.04197	0.582
	Hypothermia	0.3257	0.06312	

[Table/Fig-1]: Preoperative blood parameters.

		Groups		Total	p-value
		Normothermia	Hypothermia		
-	Count	20	13	33	0.069
	% within MAPCA(+/-)	60.6%	39.4%	100.0%	
	% within GROUPS	66.7%	43.3%	55.0% of all patients	
+	Count	10	17	27	
	% within MAPCA(+/-)	37.0%	63.0%	100.0%	
	% within GROUPS	33.3%	56.7%	45.0% of all patients	
	Count	30	30	60	

[Table/Fig-2]: Presence/Absence of MAPCAs.

Mean duration of surgery in the normothermic group was 4.22±1.006 hours. In the hypothermic group the mean duration of surgery was 5.13±1.050 hours (p-0.001) and this difference was statistically significant [Table/Fig-3].

	Groups	Mean	Std. Deviation	p-value
Duration of surgery (Hours)	Normothermia	4.22	1.006	0.001*
	Hypothermia	5.13	1.050	

[Table/Fig-3]: Duration of surgery comparison.

The need for vasopressors, presence of arrhythmias, need for DC shock, presence of haemolysis, intra and post-operative blood sugar levels, mean duration of ventilation, incidence of delayed extubation and inotropic scores for the two groups have been provided in the [Table/Fig-4-9]. The incidence of delayed extubation was more common in the hypothermia group which was statistically significant. Rest of the parameters were comparable.

There was no effect on the CPB temperature on the intra-operative and post-operative ABG reports.

The coagulation parameters and the post-operative transfusion requirements have been summarised in [Table/Fig-10]. Apart from the transfusion of FFP, the two groups were similar in their results.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	27	29	56	0.301
	% with in N	48.2%	51.8%	100.0%	
	% with in groups	90.0%	96.7%	93.3% of all patients	
Y	Count	3	1	4	
	% with in Y	75.0%	25.0%	100.0%	
	% with in groups	10.0%	3.3%	6.7% of all patients	
	Count	30	30	60	

[Table/Fig-4]: Comparison of need for intraoperative vasoactive agents.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	28	26	54	0.389
	% with in N	51.9%	48.1%	100.0%	
	% with in groups	93.3%	86.7%	90.0% of all patients	
Y	Count	2	4	6	
	% with in Y	33.3%	66.7%	100.0%	
	% with in groups	6.7%	13.3%	10.0% of all patients	
	Count	30	30	60	

[Table/Fig-5]: Presence/Absence of Post CPB arrhythmias.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	28	26	54	0.389
	% within N	51.9%	48.1%	100.0%	
	% within groups	93.3%	86.7%	90.0% of all patients	
Y	Count	2	4	6	
	% within Y	33.3%	66.7%	100.0%	
	% within groups	6.7%	13.3%	10.0% of all patients	
	Count	30	30	60	

[Table/Fig-6]: Need for post CPB DC shock.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	29	26	55	0.161
	% within N	52.7%	47.3%	100.0%	
	% within groups	96.7%	86.7%	91.7% of all patients	
Y	Count	1	4	5	
	% within Y	20.0%	80.0%	100.0%	
	% within groups	3.3%	13.3%	8.3% of all patients	
	Count	30	30	60	

[Table/Fig-7]: Presence/Absence of haemolysis.

The post-operative blood parameters were also not statistically significant when compared between the groups [Table/Fig-11].

The mean post-operative MPI for LV and RV along with difference from the preoperative values, mean number of post-operative ICU stays, incidence of prolonged ICU stay, need for re-exploration, hourly drain output, fever, mean number of days of post-operative hospital stay as well as incidence of prolonged hospital stay have been documented in the [Table/Fig-12-18]. None of the patients had surgical site infection in either group. There was significantly better post-operative RV function in the normothermia group.

	Groups	Mean	Std. Deviation	p-value
Intraoperative mean blood sugar level (mg/dL)	Normothermia	143.775	33.2773	0.148
	Hypothermia	131.307	32.5999	
Post-operative mean blood sugar level (mg/dL)	Normothermia	129.29	20.961	0.949
	Hypothermia	129.64	21.381	
Duration of ventilation (Hours)	Normothermia	11.43	12.070	0.092
	Hypothermia	18.10	17.139	
Mean vasoactive inotrope index	Normothermia	12.228	6.5393	0.102
	Hypothermia	15.457	8.4093	

[Table/Fig-8]: Comparison of blood sugar levels, duration of mechanical ventilation and vasoactive inotrope score.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	17	7	24	0.018
	% within N	70.8%	29.2%	100.0%	
	% within groups	56.7%	23.3%	40.0% of all patients	
Y	Count	13	23	36	
	% within Y	36.1%	63.9%	100.0%	
	% within groups	43.3%	76.7%	60.0% of all patients	
	Count	30	30	60	

[Table/Fig-9]: Incidence of delayed extubation.

	Groups	Mean	Std. Deviation	p-value
Post-operative act (Seconds)	Normothermia	135.83	58.777	0.700
	Hypothermia	131.10	32.167	
Post-operative platelet function	Normothermia	2.663	0.8712	0.576
	Hypothermia	2.520	1.0921	
Number of FFP transfused	Normothermia	0.20	0.761	0.015*
	Hypothermia	0.83	1.147	
Number of PC transfused	Normothermia	0.87	1.814	0.400
	Hypothermia	1.23	1.524	
Number of PRBC transfused	Normothermia	0.40	0.814	0.130
	Hypothermia	0.73	0.868	

[Table/Fig-10]: Post-operative coagulation parameters and transfusion requirements.

Post-operative	Groups	Mean	Std. Deviation	p-value
HB (g/dL)	Normothermia	11.390	1.8029	0.166
	Hypothermia	12.043	1.8020	
TLC (/cumm)	Normothermia	13986.67	4025.842	0.729
	Hypothermia	13623.33	4068.608	
Platelets (X 1000/cumm)	Normothermia	131.30	27.628	0.736
	Hypothermia	135.30	58.438	
Urea (mg/dL)	Normothermia	26.57	11.063	0.680
	Hypothermia	27.62	8.399	
Creatinine clearance (Ml/min)	Normothermia	62.737	34.5784	0.296
	Hypothermia	72.870	39.5883	
Bilirubin (mg/dL)	Normothermia	1.012	0.6885	0.549
	Hypothermia	1.135	0.8727	
INR	Normothermia	1.240	0.1657	0.181
	Hypothermia	1.400	0.6261	

[Table/Fig-11]: Post-operative blood parameters.

Besides the normothermia group had less duration of post-operative ICU stay.

Post-operative MPI				
	Groups	Mean	Std. Deviation	p-value
LV	Normothermia	0.3720	0.06609	0.554
	Hypothermia	0.3827	0.07244	
RV	Normothermia	0.382	0.1119	0.011*
	Hypothermia	0.457	0.1111	
Difference in MPI				
LV	Normothermia	0.0170	0.04324	0.445
	Hypothermia	0.0267	0.05358	
RV	Normothermia	0.0637	0.10240	0.014*
	Hypothermia	0.1313	0.10477	

[Table/Fig-12]: Post-operative MPI for LV and RV.

	Groups	Mean	Std. Deviation	p-value
Post-operative ICU stay (Days)	Normothermia	3.24	1.327	0.002*
	Hypothermia	4.62	1.840	
Post-operative hospital Stay (Days)	Normothermia	8.69	1.815	0.377*
	Hypothermia	11.34	3.015	

[Table/Fig-13]: Post-operative ICU and hospital stays.

		Groups		Total	p-value
		Normothermia	Hypothermia		
Death	Count	1	1	2	0.206
	% with in death	50.0%	50.0%	100.0%	
	% with in groups	3.3%	3.3%	3.3% of all patients	
N	Count	29	26	55	
	% N	52.7%	47.3%	100.0%	
	% with in groups	96.7%	86.7%	91.7% of all patients	
Y	Count	0	3	3	
	% with in Y	0.0%	100.0%	100.0%	
	% with in groups	0.0%	10.0%	5.0% of all patients	
	Count	30	30	60	

[Table/Fig-14]: Incidence of prolonged post-operative ICU stay.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	29	28	57	0.554
	% within N	50.9%	49.1%	100.0%	
	% within groups	96.7%	93.3%	95.0% of all patients	
Y	Count	1	2	3	
	% within Y	33.3%	66.7%	100.0%	
	% within groups	3.3%	6.7%	5.0% of all patients	
	Count	30	30	60	

[Table/Fig-15]: Incidence of Re-exploration.

		Groups		Total	p-value
		Normothermia	Hypothermia		
N	Count	27	27	54	1
	% within N	50.0%	50.0%	100.0%	
	% within groups	90.0%	90.0%	90.0% of all patients	
Y	Count	3	3	6	
	% within Y	50.0%	50.0%	100.0%	
	% within groups	10.0%	10.0%	10.0% of all patients	
	Count	30	30	60	

[Table/Fig-16]: Incidence of post-operative fever.

		Groups		Total	p-value
		Normothermia	Hypothermia		
Death	Count	1	1	2	0.206
	% within death	50.0%	50.0%	100.0%	
	% within groups	3.3%	3.3%	3.3% of all patients	
N	Count	29	26	55	
	% within N	52.7%	47.3%	100.0%	
	% within groups	96.7%	86.7%	91.7% of all patients	
Y	Count	0	3	3	
	% within Y	0.0%	100.0%	100.0%	
	% within groups	0.0%	10.0%	5.0% of all patients	
	Count	30	30	60	

[Table/Fig-17]: Incidence of prolonged pos-toperative hospital stay.

Parameters	Groups	Mean	Std. Deviation	p-value
Post-operative hourly drain output per kg body weight (ml/kg/hour)	Normothermia	1.5053	0.77881	0.276
	Hypothermia	1.8147	1.33056	

[Table/Fig-18]: Post-operative drain output.

DISCUSSION

The baseline characteristics between the two groups were comparable. When the two groups were compared in this regard the mean VIS (vasoactive inotrope score) was less in the normothermic than in the hypothermic group. However, this difference was not high enough to be statistically significant. In a study involving normothermic CPB in paediatric patients, there was statistically significant difference in inotropic requirements [11]. The greater incidence of RV dysfunction associated with ICR for TOF patients perhaps was the predominant reason behind this difference in outcome.

Shamsuddin AM et al., showed that with use of normothermic high flow CPB in the paediatric age group more than 90% patients were extubated within 3 hours [11]. However, the surgeries in their study were relatively simpler than ICR. Although, our study also showed a favourable outcome with respect to duration of mechanical ventilation like their study, the greater mean duration of ventilation in either group could be attributed to the greater complexity of the surgery involved. The results of our study were however comparable to other studies published in Europe [12].

Similar studies showed that the mean duration of post-operative hospital stay was about 7.2 days with normothermic CPB [13]. Although the duration of hospital stay was less for the patients with normothermic CPB, our study population had about 1.5 days of longer hospital stay. This could possibly be attributed to poor general condition as well as greater ICU stay in our patients which was again possibly due to the nature of the surgery as well as the greater requirements of mechanical ventilation.

We saw that although the duration of ICU stay was significantly lowered by application of normothermic CPB, hypothermic CPB does not necessarily result in a prolonged ICU stay. However, even a decreased stay in the ICU by one day would mean less of a financial as well as psychological burden for the patients and their guardians and hence application of normothermic CPB will be welcome in this regard. When we compared the results with other similar studies, although our study showed similar trends in the outcomes, the mean duration of ICU stay in the normothermic group was higher in our group (3.24 vs 2.7) [11]. The patient population in our study were operated for TOF and showed varied degrees of RV dysfunction post-operatively which increased the dose and duration of inotropic support post-operatively along with increased mechanical ventilation. Both these factors could possibly have resulted in the greater duration of ICU stay in our study population.

In terms of creatinine clearance the results of our study were comparable to the study of Xiong Y et al., [14]. Provenchere S et al., also had not found any correlation between CPB temperature and renal dysfunction in their study [15].

Bleeding is an inherent risk factor having a major impact on patient prognosis in cardiac surgery. Cyanotic patients exhibit a greater degree of platelet dysfunction which leads to increased blood loss. We hence tried to analyse the effect of CPB temperature on this vital parameter. Since the patients had wide range of body weights we decided to compute the hourly drain output per kg body weight. Bleeding was not significantly different. Thus, we concluded that as long as re-warming post CPB was complete, the CPB temperature did not have a significant effect on the volume of post-operative blood loss. When the two groups were thus compared requirement of FFP was significantly more with the hypothermic group. However, no differences were found in terms of PC and PRBC requirements. We could not find any similar study to have assessed this parameter in their groups.

Varying degrees of RV dysfunction was noted in almost all the patients while LV function was more or less preserved. When these data were compared in between the two groups, hypothermic CPB was found to be associated with a greater degree of RV dysfunction. Especially in a surgery like ICR for TOF where the patients are at a greater risk of RV dysfunction, this difference was of immense importance from the clinical perspective. However, in the patients requiring transannular patch for their repair which were more in the hypothermia group, the degree of RV dysfunction is usually greater, and this could have acted as a potential source of bias in this assessment. This parameter again had not been assessed in prior studies.

ABGs had been performed on the patients at several points during the course of surgery and post-operatively. We had taken up the parameters of pH, bicarbonate and base excess to assess the degrees of, metabolic acidosis and their normalisation. However when the two groups were compared in this regard, the differences were not statistically significant. Xiong Y et al., had used lactate levels to compare the levels of metabolic acidosis [14]. But all in all, our results were similar to theirs.

Lehot JJ et al., in their study showed that blood sugar rise was evident in patients with both normothermic and hypothermic CPB [16]. We in our study also noted similar derangements in blood sugar levels in the entire study population irrespective of the CPB temperature. However in our study, we did not measure serum insulin level, which was also seen to rise proportionately with the rise in blood sugar levels in the normothermic group in their study [16].

We compared the mean values of ACT and platelet function in the two groups. Similar to transfusion requirements, no gross difference was found between the two groups in this regard. Although several patients in both the groups did have a deranged platelet function, the almost uniform distribution of them in the two groups suggested that it could be a result of the primary background of cyanotic heart disease. Similar studies had not compared this parameter.

Haemolysis is one of the important side effects of CPB. This not only affects the renal function of the patients but can also lead to increased morbidity. Although the individual numbers were different, this difference was not statistically significant.

The increased duration of surgery in the hypothermia group could be possibly attributed to the time required to completely re-warm the patients in the hypothermia group. None the less, a decreased duration of surgery with decreased anaesthesia time is obviously significant especially in the background of patients falling in the paediatric age group with increased hazards of general anaesthesia. In this regard the outcome of our study was in a way contrary to what was seen in the study performed by Xiong Y et al., [14].

LIMITATION

It was a small study with a study population of 60 patients. Patients were operated by different surgeons. Besides, this was a retrospective, observational study.

CONCLUSION

From the results of our study we concluded that ICR for TOF under normothermic CPB is feasible. Normothermic CPB resulted in better patient outcomes in terms of reduced post-operative ICU and hospital stay, lesser incidence of delayed extubation and post-operative RV dysfunction and lesser transfusion requirements of FFP. There was no impact of the CPB temperature on renal function, mean blood sugar levels, coagulation parameter and post-operative drain output, post-operative fever, wound infection, arrhythmia and need for re-exploration. For us, the outcomes have implied that if the intracardiac return can be manageable by proper venting, performing ICR for TOF using normothermic CPB can be attempted and this might result in better post-operative results in certain aspects. Besides, since our study is limited by small number of subjects as well retrospective nature, further studies can be conducted in the form of randomised control trials on a larger study population which would definitely give us more convincing results and more definitive conclusions can be reached on the topic.

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