Acta Anaesth. Bel., 2026, 77 (3): *219-226*

Original study

The metabolic effect of 7,5% icodextrin vs 0,9% NaCl as carrier solutions for chemotherapy drugs in HIPEC procedures

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Abstract

Objectives: Glucose-containing solutions are commonly used as carrier fluids during hyperthermic intraperitoneal chemotherapy (HIPEC) but concerns regarding hyperglycaemia and possible associated infection risks have led to the use of isotonic crystalloids as an efficient alternative. However, to date the metabolic implications of these alternatives remain largely unexplored. This study compares the metabolic effects of different HIPEC carrier solutions, namely a carbohydrate dialysate: 7,5% icodextrin and 0,9% NaCl solution.

Methods: We conducted a single-centre, retrospective, propensity-matched cohort study including 34 patients undergoing cytoreductive surgery (CRS) with HIPEC, in which the carrier solution for the chemotherapy drugs was either 0.9% NaCl (n = 17) or 7.5% icodextrin (n = 17). Blood analyses were performed after induction of anaesthesia, immediately postoperatively upon ICU admission and on postoperative day one. Intraoperative fluid and electrolyte substitution and postoperative insulin administration were recorded. Clinical outcomes included the duration of invasive ventilation and postoperative hemodynamic support.

Results: Glycaemic levels were slightly higher in the icodextrin group but this was not statistically significant. Insulin administration was significantly higher in this cohort. Both groups developed metabolic acidosis which resolved on post op day one. In the icodextrin group this was attributed to significant hyperlactatemia. The 0,9% NaCl group showed a hyperchloremic metabolic acidosis, confirmed by a low strong ion difference on Stewart analysis and characterized by significantly reduced plasma bicarbonate and CO_2 levels. Potassium chloride supplementation was significantly higher in the icodextrin group, sodium bicarbonate and potassium phosphate use were comparable. No differences in vasopressor and ventilatory support were observed.

Conclusions: HIPEC carrier solutions exert significant and distinct perioperative metabolic effects. Glucose-containing solutions, namely 7.5% icodextrin, induce hyperlactatemic acidosis requiring increased insulin and concomitant potassium supplementation. 0,9% NaCl induced a more profound and longer hyperchloremic metabolic acidosis likely due to peritoneal chloride absorption. Further research should consider systemic perioperative metabolic derangements and their potential impact on postoperative outcomes when selecting the optimal HIPEC carrier solution during CRS.

Key words: **HIPEC, cytoreductive surgery, perioperative care, carrier solution, blood glucose, acid-base imbalance.**

The authors confirm that this manuscript has not been published elsewhere and is not under consideration by any other journal. All authors have approved the manuscript, contributed significantly and have no conflicts of interest to declare. No funding was received for this research. Ethical approval by the local ethics committee study was obtained for this retrospective at ZOL Genk, Synaps Park 1, 3600 Genk, Belgium.

Introduction

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is a specialized treatment modality utilized in the management of both primary peritoneal malignancies and secondary peritoneal metastases of digestive and ovarian malignancies[1]. Heated chemotherapy, which is dissolved in a carrier solution, is directly poured into the abdominal cavity following complete cytoreductive surgery (CRS), with the aim of eradicating residual microscopic cancer cells and minimizing the risk of disease recurrence. While HIPEC has demonstrated efficacy in improving survival outcomes for selected patients, its use is often accompanied by various metabolic and physiological challenges during the peri-operative time-period. These include hyperglycaemia, acidosis and electrolyte disturbances. The dialysate and the temperature of the dialysate used during HIPEC has a role in contributing towards these challenges[2-5].

The pathophysiology of metabolic acidosis during and after HIPEC procedures needs further clarification and the role of carrier solutions in inducing metabolic acidosis has not yet been extensively studied. A limited number of studies have suggested a link between the metabolic derangements and complications after HIPEC procedures, suggesting that managing these metabolic disturbances might be of clinical significance[4,7,8]. While most studies have focused on the role of these carrier solutions on the hyperglycaemic response after HIPEC surgery, case reports suggest that the type of carrier solution could be of significance in the cause of metabolic acidosis[9]. 7.5% icodextrin is a glucose polymer developed for peritoneal dialysis providing a lower carbohydrate load and superior ultrafiltration than dextrose solutions, especially in patients with high membrane transport rates or fluid overload. It offers a better biocompatibility, reduces glucose exposure and improved blood pressure control[10,11].

In this retrospective study, we aimed to investigate the metabolic effects of two different HIPEC carrier solutions (0.9% NaCl and 7.5% icodextrin) in a propensity score-matched cohort, with particular focus on acid-base disturbances (including metabolic acidosis) during CRS.

Methods

Design of the retrospective cohort

Ethical approval for this retrospective study was obtained from the local ethics committee of the ZOL hospital, Genk, Belgium. As this was a retrospective study, informed consent was not deemed necessary by the committee.

We performed a single centre retrospective propensity matched cohort study. Patients who underwent CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) at the ZOL hospital in Genk, Belgium, between January 2016 and April 2017 and between January 2022 and April 2023 were included. These time frames were chosen because during these periods most procedures were performed by the same surgeon using a closed HIPEC technique with simultaneous intravenous (IV) chemotherapy, both according to a standardised protocol, hereby reducing any inter operator bias. Patients were excluded from this cohort of patients if patient data, parameters or medication were not recorded electronically, if blood analyses weren't performed on the timepoints of interest, if the type of carrier solution wasn't properly noted or if the main operator was a different person than the mentioned surgeon. Next, patients were matched for age, sex, BMI, baseline creatinine and duration of surgery, this last to account for severity of surgical stress. Furthermore, patients were matched for intraoperatively administered intravenous amount of 0,9% NaCl , balanced crystalloids (Plasma-Lyte and Hartmann) and colloids (Volulyte) to minimize bias in investigating the metabolic effect of the administered peritoneal carrier solution.

HIPEC was performed with a carrier solution, used intraperitoneally, consisting of either a 7.5% icodextrin dialysate or 0,9% NaCl. Patients were assigned to two cohorts according to the type of carrier solution used: a 7,5% icodextrin cohort, and a 0,9% NaCl cohort.

Perioperative protocol

During anaesthesia and intensive care, lung protective ventilation targeting normocapnia was applied unless hyperventilation was deemed necessary for respiratory compensation of metabolic acidosis. Hemodynamic stability was maintained using goal directed fluid therapy and IV infusion of norepinephrine. Beyond predefined investigated time points arterial blood gas sampling rate and corrective interventions were performed at discretion of the treating physician. Blood glucose levels were targeted < 180 mg/dl as per institutional protocol. Anaesthetic management followed standard clinical practice and was left at discretion of the treating anaesthesiologist, thereby reflecting clinical practice, however all patients received thoracic epidural analgesia. Chemotherapeutic drugs were selected during a pre-operative multidisciplinary meeting. Drugs used were cisplatin and doxorubicin with IV ifosfamide, oxaplatin with IV fluorouracil or mitomycin with IV fluorouracil. Peritoneal dialysate was perfused

at an elevated temperature of 41 to 43 degrees Celsius during 30 minutes for oxaplatin and 90 minutes for cisplatin and doxorubicin or mitomycin. Postoperatively, patients were evaluated for extubation by an intensive care physician when hemodynamically and metabolically stable without the need for prolonged mechanical ventilation or airway protection.

Investigated variables

Baseline characteristics investigated were age, sex, BMI and duration of surgery, intraoperatively administered intravenous amount of 0,9% NaCl, balanced crystalloids (Plasma-Lyte and Hartmann) and colloids (Volulyte).

Since the main topic of interest was the metabolic response to the carrier solution, several blood analyses were evaluated on three time points, being 1. after induction (before CRS and HIPEC), 2. direct post-operatively (upon arrival at the ICU) and 3. the morning after surgery (morning blood analyses on ICU).

Concerning glucose metabolism, we evaluated glycaemia on the different timepoints and the administered dose of insulin in the first 24 hours after surgery. Concerning acid-base metabolism, we evaluated following parameters on mentioned timepoints: pH, bicarbonate, plasma CO2 and strong ion difference (SID). Apparent and effective strong ion difference (SID) were calculated according to the Stewart approach using following formulae:

SID apparent was calculated using formula: [Na] + [K] + [iCa] + [Mg] – [Cl] – [Lact] with all variables in mmol/L.

SID effective was calculated using formula: [Bic] + [Alb] x [(0.123 x pH) – 0.631] + [Pho] x [(0.309 x pH) – 0.469] with Bic in mmol/L, Alb in g/L and Pho in mmol/L.

Measured clinical outcomes were duration of invasive ventilation and hemodynamic support necessary. Hemodynamic support was measured as total amount of norepinephrine in milligram infused postoperative over the first 24 hours. The intraoperatively administered amount of potassium chloride (KCl, in mEq), potassium phosphate (KPO4, in mEq), sodium bicarbonate ($NaHCO_2$, in ml) and albumin (in ml) were recorded separately.

Statistics

Statistical analysis of the data was performed using JMP Pro, version 17 software (SAS Institute, Cary, NC, USA). Categorical data are represented as numbers and proportions and are compared by a Chi-square test. The distribution of continuous data was analyzed, represented as either mean +/− SD or median and IQR and compared by Student t-test or Mann-Whitney U-test, respectively, depending on their normality of distribution. Neither multiple data imputation for missing values, nor correction for multiple testing was done. For each test, a two-sided p-value ≤0.05 was considered statistically significant.

Results

Development of the cohort and baseline characteristics

We identified 65 patients undergoing CRS with HIPEC between January 2016 and April 2017 and between January 2022 and April 2023. 13 patients were excluded for following reasons: for 6 patients there was no electronical registration intra-operatively, 5 patients had missing data/inadequate blood analyses and in 2 patients the procedure was performed by a junior surgeon under supervision, resulting in longer operation duration. This resulted in 52 patients. After propensity matching based upon age, sex, BMI, baseline creatinine, duration of surgery and amount of fluid administered (0,9% NaCl, crystalloids and colloids) a total of 34 patients was identified with 17 in the 0,9% NaCl and 17 in the 7,5% icodextrin cohort. Figure 1 shows patient selection.

Baseline characteristics are shown in Table I and were similar between both cohorts.

Markers of glucose dyshomeostasis

Glycaemia on several timepoints was assessed, namely upon induction, upon arrival at the ICU and the morning after surgery. Furthermore, we evaluated the dose of administered insulin in the 24 hours following operation. Due to lack of reliable data, the dose of insulin intraoperatively couldn't be reliably assessed.

Glycaemia was comparable upon induction and rose more in the 7,5% icodextrin group than in the 0,9% NaCl group, with a mean increase in the 7,5% icodextrin group being 36 mg/dl (SD 38) and in the 0,9% NaCl group 18 mg/dl (SD 21), however the difference proved not to be statistically significant (P=0.1). The number of units of insulin administered during the first 24 hours after surgery was significantly higher in the 7,5% icodextrin group as compared to the 0,9% NaCl group (Table II).

Markers of acid base metabolism

Immediately postoperatively, upon admission in the ICU, we found no significant difference in pH, however, both groups had a slightly acidic pH upon admission in the ICU (Table III). There was

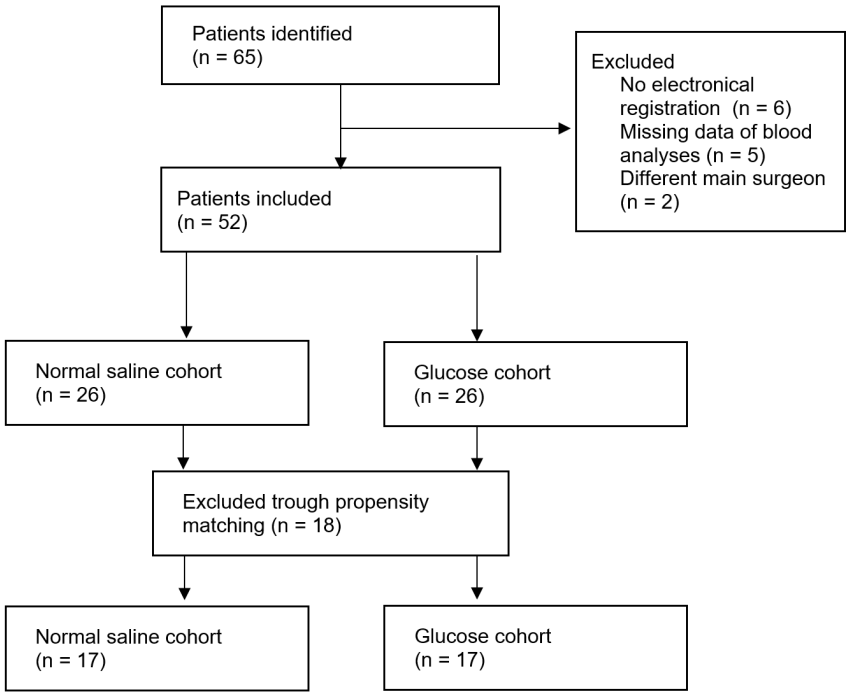

Fig. 1 — Patient selection process.

Table I. — Baseline demographic and perioperative characteristics.

	7,5% icodextrin	0,9% NaCl	P-value
Age (years)	57 (11)	61 (11)	0.30
Sex, males, n (%)	5 (29)	10 (58)	0.16
BMI (kg/m²)	25 (3.42)	25 (5.04)	0.72
Baseline creatinine (mg/dL)	0.82 (0.14)	0.87 (0.18)	0.37
Duration of surgery (hours)	7.04 (1.83)	7.26 (1.70)	0.71
Intraoperative amount of administered 0,9% NaCl (ml)	500 (637)	735 (437)	0.21
Intraoperative amount of administered balanced crystalloids (ml)	3941 (2006)	3176 (1144)	0.18
Intraoperative amount of administered colloids (ml)	352 (424)	147 (293)	0.10
Total amount of administered intravenous solutions (ml)	4794 (1696)	4058 (1073)	0.14
Data are presented as mean (SD) unless otherwise specified.			

Table II. — Perioperative blood glucose values at predefined time points and insulin administration.

Glycaemia	7,5% icodextrin	NaCL	P Value
Induction (mg/dl)	104.6 (12.3)	108.6 (14.8)	0.40
Arrival on IC (mg/dl)	140.9 (42.8)	126.8 (18.0)	0.22
Postop day one (mg/dl)	145.6 (39.5)	140.5 (17.9)	0.63
Total insulin postoperative, median (IQR) (U)	4 (0;23.15)	0(0;0)	0.05
Data are presented as mean (SD) unless otherwise specified.			

a significant lower plasma CO_2 in the 0.9% NaCl cohort, consistent with therapeutic hyperventilation aimed at correcting acidemia. Bicarbonate was also significantly lower in the 0,9% NaCl cohort, as compared to the 7,5% icodextrin group. Notably, the chloride levels were significantly higher in the 0,9% NaCl group than in the 7,5% icodextrin group, as were the potassium levels. The lactate concentration on the other hand, was higher in the 7,5% icodextrin group than in the 0,9% NaCl group. This resulted in a higher apparent and effective SID in the 7,5% icodextrin cohort as compared to the 0,9% NaCl cohort. There was no significant difference in sodium concentration.

On post op day one we found no significant difference in pH which was normalized in both groups. No significant difference in bicarbonate, lactate and CO_2 was apparent. However, chloride

Table III. — Blood gas parameters, lactate, electrolytes, and strong ion difference (SID) at predefined time points.

	7,5% icodextrin	0,9% NaCl	P-value
pH (7.35-7.45)			
Induction	7.36	7.37	0.39
Arrival on ICU	7.31	7.33	0.23
Postop day one	7.38	7.36	0.40
pCO2 (35-45 mmHg)			
Induction	36.09	39.72	0.02
Arrival on ICU	42.8	36.29	0.003
Postop day one	40.91	39.95	0.63
Bicarbonate (22-26mmol/L)			
Induction	19.72	22.92	0.0003
Arrival on ICU	21.17	18.69	0.02
Postop day one	23.71	22.14	0.06
Lactate (1-1.5 mmol/L)			
Induction	0.81	0.69	0.13
Arrival on ICU	2.42	0.82	<0.0001
Postop day one	1.62	1.38	0.30
Sodium (136-146 mmol/L)			
Induction	139.88	141.53	0.009
Arrival on ICU	142.82	142.06	0.33
Postop day one	141.41	141.41	1.00
Potassium (3.5-5.0 mmol/L)			
Induction	3.31	3.5	0.17
Arrival on ICU	3.62	4.30	<0.0001
Postop day one	3.96	4.11	0.20
Chloride (96-107 mmol/L)			
Induction	102.82	102.94	0.87
Arrival on ICU	109	113.06	0.002
Postop day one	107.53	110.88	0.004
SID apparent (38-42 mmol/L)			
Arrival on ICU	36.98	34.33	0.02
Postop day one	38.16	35.28	0.004
SID effective (24-28 mmol/L)			
Arrival on ICU	23.35	21.19	0.04
Postop day one	26.55	25.06	0.10

Data are presented as mean.
Strong ion difference (SID) apparent was calculated using formula: [Na] + [K] + [iCa] + [Mg] – [Cl] – [Lact] with all variables in mmol/L.
SID effective was calculated using formula: [Bic] + [Alb] x [(0.123 x pH) – 0.631] + [Pho] x [(0.309 x pH) – 0.469] with Bic in mmol/L, Alb in g/L and Pho in mmol/L.

content was still higher in the 0,9% NaCl group as compared to the 7,5% icodextrin group, resulting in a higher apparent SID.

Peri-operatively there was no significant difference in $NaHCO_2$ and KPO_2 supplementation between both cohorts. We did record a marginally significant higher intraoperative KCl administration in the 7,5% icodextrin cohort with a mean 22.35 mEq vs 8.23 mEq for the 0,9% NaCl cohort (p=0.0485) during surgery (Table IV).

Effect on vasopressor support and duration of ventilatory support

The amount of norepinephrine administered in the first 24 hours after surgery was similar with a mean dose of 2.85 mg (SD 3.28) in the 7,5% icodextrin group vs 2.09 mg (SD 2.74) mg in the 0,9% NaCl group (p=0.45).The duration of invasive ventilation after surgery was similar between both groups with a mean 11.64 hours (SD 4.58) in the 7,5%

Table IV. — Substitution during OR.

	7,5% icodextrin	NaCl	P
KCl (mEq)	22.35	8.23	0.05
$NaHCO_2$ 8.4% (ml)	23.53	29.41	0.71
KPO_2 (mEq)	0	2.35	0.33
Data are presented as mean.			

icodextrin group and 11.10 (SD 6.01) in the 0,9% NaCl group (P=0.76).

Discussion

This study demonstrates that different carrier solutions used in HIPEC procedures exert significant effects on perioperative metabolism. 7,5% icodextrin was associated with lactic acidosis and required increased perioperative insulin administration to adjust for hyperglycemia, with a concomitant increased need for potassium supplementation likely due to an intracellular shift mediated by insulin. The use of 0.9% NaCl resulted in a more pronounced hyperchloremic metabolic acidosis, potentially due to peritoneal chloride absorption.

While both solutions gave rise to an acidic state after HIPEC, the underlying mechanism differed substantially. In the 0,9% NaCl group a profound metabolic hyperchloremic acidosis was observed for which therapeutic ventilator hyperventilation was necessary. This was characterized by increased plasma CO_2 and bicarbonate levels and confirmed on a Stewart analysis with a low strong ion difference caused by hyperchloremia. There difference in IV NaCl 0.9% infusion between groups was small and not significant. It's associated with hyperchloremic acidosis when infusion is rapid and includes large volumes, FDA labelling warns for infusions larger than one liter[12,13].

The 7,5% icodextrin group induced a less pronounced metabolic acidosis with hyperlactatemia, likely due to increased lactate formation by stimulation of glycolysis[14,15]. No effects on clinical outcomes were found with no difference in vasopressor or ventilatory support, most likely due to the limited sample size. However, the hyperchloremia persisted longer than the hyperlactemia, suggesting a more prolonged metabolic derangement when using 0,9% NaCl as a carrier solution.

The ideal HIPEC carrier solution provides high exposure to cytotoxic agents, prolonged intraperitoneal volume, slow peritoneal clearance and absence of local adverse effects. Hypotonic solutions caused thrombocytopenia and a high incidence of bleeding were observed. Hypertonic solutions slowed clearance of intraperitoneal fluid but resulted in dilution and poor tumor penetration. Isotonic high molecular weight solutions such as 7,5% icodextrin appeared more appropriate due to slower peritoneal clearance and high intraperitoneal volume[10,16,17]. A 2006 expert statement, where consensus was obtained through a Delphi process at the Fifth International Workshop on Peritoneal Surface, recommended isotonic salt solutions and dextrose-based carriers, with 6% of experts favoring isotonic high molecular weight solutions and 41% calling for further research[18]. The 2022 PSOGI international consensus now recommends 0,9% NaCl solutions for cisplatin regimens. For oxaliplatin regimens 45.8% preferred dextrose solutions, although no clear consensus was reached[19].

Intraperitoneal chemotherapy is based on pharmacologic principles for peritoneal dialysis, typically fluids with high glucose concentration. Due to concerns over oxaliplatin instability in chloride-rich environments, 5% dextrose was used as carrier solution. However, more recent in vitro research demonstrated only limited degradation in the time frame for HIPEC and degradation was associated with formation of the active cytotoxic drug form of oxaliplatin[6,20]. Due to the concern of hyperglycemia and its possible associated risk of infectious complications, several authors suggest the use of isotonic saline solutions[21].

Clinical practice switched to 0,9% NaCl solutions, however, there are no large RCTs available confirming it's clinical superiority. While we observed no significant difference in glycaemic levels, insulin requirements were higher with 7,5% icodextrin. Furthermore, hyperchloremic metabolic acidosis has been suggested to be detrimental, possibly leading to acute kidney injury and prolonged mechanical ventilation due to respiratory compensation. Therefore, further research is needed and should focus on the clinical effects of different carrier solutions. From this point of view, investigating the potential beneficial role of a balanced crystalloid solution as carrier solution is especially interesting. Our study adds to recent simultaneous work by Argin et al attributing changes in electrolytes to different carrier solutions[22] however our data provides a

more in depth metabolic examination regardless of chemotherapeutic agent.

We report several limitations in our study. Notably, the non-randomized retrospective design introduces potential temporal bias caused by using data from two different time periods. Additionally, we acknowledge the small size of our patient sample. A strict propensity matching method was used to address these issues, matching for fluid administration to minimise differences between time periods while anaesthesiologic protocol remained the same. Due to lack of information, no matching was possible for surgical or pathology-related factors. Despite these limitations, excluding procedures performed by other surgeons eliminates inter operator variability. Relying on electronically registered data ensured precision and reduced documentation bias offering a more superior level of detail than handwritten medical charts. However, both did decrease our sample size.

In conclusion, our findings show that carrier solutions during HIPEC procedures induce profoundly different metabolic effects, particularly in acid–base balance. While 7.5% icodextrine induces lactic acidosis and increased insulin need, 0.9% NaCl resulted in a more severe and persistent hyperchloremic metabolic acidosis. Further research should consider these metabolic derangements and their potential impact on postoperative outcomes when selecting the optimal HIPEC carrier solution during CRS.

Funding: No funding was received for this research.

Declaration of competing interest: The authors declare that they have no known financial or other competing interests.

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doi.org/10.56126/77.3.24