European Journal of Surgical Oncology 50 (2024) 107955

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Eliminating the need for preoperative intravenous hyperhydration: Sodium thiosulfate as nephrotoxicity prevention in HIPEC-treated patients – A retrospective analysis

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A B S T R A C T

Background: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment for peritoneal metastases. However, HIPEC with cisplatin is associated with renal toxicity. Sodium thiosulfate (ST) has been shown to prevent cisplatin-induced toxicity.

Methods: A retrospective, single-center analysis of patients treated curatively for peritoneal surface malignancy, who underwent cytoreductive surgery with cisplatin-based HIPEC between 2015 and 2020. Patients were categorized into three groups based on the management of cisplatin-induced renal toxicity: preoperative hyperhydration alone (PHH), preoperative hyperhydration with ST (PHH + ST), and ST alone. Renal function and complications, in terms of Acute (AKI) and chronic kidney injury (CKI), were monitored and analyzed during 3 postoperative months.

Results: This study included 220 consecutive patients. Mean serum creatinine levels were 95, 57 and 61 mmol/L, for PHH, PHH + ST and ST groups, respectively ($p < 0.001$). Glomerular Filtration Rate (GFR) were 96, 94 and 78 ml/min/1.73 m^2, respectively ($p < 0.001$). AKI and CKI are respectively for PHH, PHH + ST and ST groups were 21 % (n = 46), 1 % (n = 2) and 0 % vs 19 % (n = 42), 0 % and 0 % ($p < 0.001$), for pairwise analysis did not show any difference between PHH + ST and ST alone combination, regarding nephrological outcomes. All patients were followed 3 months postoperatively.

Conclusion: There is no need for preoperative hyperhydration when sodium-thiosulfate is used to prevent cisplatin-induced nephrotoxicity in patients undergoing cytoreductive surgery with HIPEC. These findings have implications for improving and simplifying the management of patients with peritoneal metastases undergoing HIPEC with cisplatin.

Key messages

What is already known on this topic:

- Cisplatin-based HIPEC is effective for peritoneal metastases but poses renal toxicity risks.
- Preoperative hyperhydration is a common practice to condition the kidneys before exposure to nephrotoxic agents in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC).
- Sodium thiosulfate (ST) has shown potential in preventing cisplatin-induced nephrotoxicity.

What this study adds:

- ST alone effectively prevents renal toxicity in HIPEC, making preoperative hyperhydration unnecessary.

How this study might affect practice:

- Reevaluation of preoperative hyperhydration protocols may be prompted by these findings.
- ST as a renoprotective strategy may enhance the safety and efficiency of cisplatin-based HIPEC.

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https://doi.org/10.1016/j.ejso.2024.107955
Received 26 November 2023; Accepted 5 January 2024
Available online 6 January 2024

1. Introduction

Cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy (HIPEC) has become an essential treatment for peritoneal metastases. Peritoneal metastases are the natural evolution of most cancers of the digestive tract as well as gynecological cancers, with the highest incidence in ovarian cancer [1,2]. The rationale of HIPEC is not only based on the direct cytotoxic effect of heat on cancer cells but also because it enhances the effectiveness of selected chemotherapy molecules (thermal potentiation) [3].

Cisplatin is one of the most commonly used drugs for HIPEC and is effective in treating primary peritoneal cancers and peritoneal metastases of ovarian or endometrial origin [2,4–7]. Cisplatin is used according to different protocols, either alone, as in the Dutch OVHIPEC trial by Van Driel et al. or in combination with other molecules such as mitomycin C or doxorubicin [2].

Cisplatin is known to cause renal failure, whether administered systemically or intraperitoneally [8]. Because of its renal excretion it can accumulate in the proximal renal tubules and lead to nephrotoxicity. In clinical practice, the overall prevalence of nephrotoxicity induced by cisplatin involves about one-third of patients when administered intravenously [9]. The renal toxicity of intraperitoneal cisplatin has a similar mechanism, with acute renal failure in up to 40 % of patients, which may lead to chronic renal failure in up to 4 % of patients [10–13].

Intravenous hydration significantly reduces the half-life of cisplatin, its urinary concentration, and its transit time in the proximal tubules, and may be combined with other treatments such as mannitol or furosemide to prevent renal toxicity [14,15]. It should be carried out over a short period (2–6 h) and be diluted with 2–4 L of hydration [9].

Sodium thiosulfate (ST) has been used for several years in the prevention and treatment of cisplatin-induced toxicity, including renal toxicity and cyanide poisoning [16–19]. It has been demonstrated to be effective as a nephroprotective agent during HIPEC with platinum-based chemotherapy in a recent prospective study [10,20,21].

We introduced its use in Center Hospitalier Lyon Sud following the results of the randomized trial from Van Driel et al. in 2 phases [2]. We first used ST in combination with preoperative hyperhydration (PHH) and a second phasis without PHH. Our study aimed to evaluate the effort of PHH in combination with sodium thiosulfate in preventing nephrotoxicity induced by intraperitoneal cisplatin in patients who have undergone cytoreductive surgery with HIPEC.

2. Material and methods

2.1. Study population

We conducted a retrospective, single-center analysis at Center Hospitalier de Lyon Sud. The study included all patients with peritoneal metastases, who underwent cytoreductive surgery with cisplatin-based HIPEC between January 01, 2015, and July 30, 2020. We categorized the patients into three study groups, corresponding to three consecutive periods, for the management of cisplatin-induced renal toxicity. One group received preoperative hyperhydration alone (PHH), the second one received preoperative hyperhydration with the addition of ST (PHH + ST), and a third one received sodium thiosulfate alone (ST). All concerned patients received ST after obtaining a “Temporary Use Authorization” (ATU) from the ANSM (French National Drug Agency).

2.2. Treatments

All patients in the study received immunonutrition for 7 days before surgery. Patients in PHH group and group 2, who received preoperative hyperhydration, were admitted to the hospital two days before surgery and received 3 L of Ringer Lactate intravenously over 24 h for 48 h. All patients in the study underwent cisplatin-based HIPEC, and the completeness of cytoreductive (CC-score) surgery was evaluated using the CC-score, as it has the most significant prognostic value compared to other score like R classification (R0/R1/R2) [22]. classification. Cisplatin was administered alone at a dose of 100 mg/m^2 or in combination with other drugs, such as doxorubicin or mitomycin C, at a dose of 50 mg/m^2. The peritoneal bath was heated to 42 °C for 60–90 min. Patients in groups 2 and 3 who received ST were given a 9 mg/m^2 intravenous bolus at the time of the first cisplatin injection, followed by a 6-h maintenance infusion of 12 mg/m^2 at the end of HIPEC, using the same protocol as the Van Driel et al. trial [2].

2.3. Data collection

We reviewed the informatic medical records to collect for all the patients: clinical data (baseline characteristics, primary tumor histology), surgical data (HIPEC-drug regimen, PCI (peritoneal cancer index or Sugarbaker score), CC-0 or CC-1/2) and postoperative data [23]. The extent of the peritoneal disease and completeness of cytoreduction were systematically assessed peroperatively and recorded according Peritoneal Cancer Index (PCI) and Cytoreduction Completeness (CC) grading according to Sugarbaker, respectively. We also analyzed the plasmatic creatinine dosage as well as the estimated glomerular filtration rate (estimated GFR according CKD-EPI formula) for each patient preoperatively and then postoperatively from day 1 to day 10 as well as at 1 month, 3 months, and 6 months [24]. Associated severe postoperative complication 90 days-days were also analyzed according to Clavien classification [25].

2.4. Statistical analysis

The proportions of baseline characteristics were compared by Pearson’s Chi [2] or Kruskal-Wallis tests, continuous and categorical variables, respectively. Changes in creatinine and glomerular filtration rate were compared between groups using linear mixed-effects models in which the subject was considered a random-effect variable and group, cisplatin dose, and use or non-use of other HIPEC drug as fixed-effect variables. Missing data were handled as-is, without resorting to computational imputation techniques. We adopted this approach to ensure transparency and data integrity throughout our analysis. Missing data were reported in our manuscript, and we assessed the potential implications of these missing data on our results. Analysis was performed using RStudio Software (RStudio: Integrated Development for R. PBC, Boston, MA, 2020). Statistical significance was reached with a two-sided p-value <0.05.

2.5. Ethical appliance

Ethical standards were meticulously upheld, and the study received prior approval from the local ethics committee (Scientific and Ethical Committee of Hospices Civils de Lyon, France). Participant data were handled with complete confidentiality, ensuring anonymity through the use of unique identifiers. Informed consent was obtained, when necessary, by ethical requirements. This section underscores our commitment to ethical research practices and compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines in our retrospective study.

3. Results

3.1. Demographic

During the study period, 230 consecutive patients underwent cytoreductive surgery (CRS) with cisplatin-based HIPEC from a single referral center. Ten patients were excluded from the analysis, as they did not receive preoperative hyperhydration or ST (see flowchart in supplementary materials Fig. S1). Baseline characteristics showed a population study essentially in the fifth decade with a predominant women

sex ratio which was comparable between groups, regarding age and comorbidity. See Table 1.

3.2. Surgical data

The surgical data showed a homogeneous population between groups regarding the extent of the peritoneal disease, with a median PCI of 9/39 (IQR 5, 14). Complete cytoreduction rate (CC-0) and CC-1 (with residual disease <2.5 mm) were high (98.6 %, n = 216) with a few patients (1.4 %, n = 3) who had uncomplete CRS. HIPEC with closed-abdomen technique was the privileged approach in our center [26]. HIPEC duration was between 60 and 90 min. HIPEC-drug regimens were mainly monodrug (63 % cisplatine). See more details in Table 2.

3.3. Kidney function analysis

Mean serum creatinine levels were 95, 61 and 57 mmol/L, for PHH, PHH + ST and ST groups, respectively (p < 0.001). See Fig. 1.

Glomerular Filtration Rate (GFR) were 96, 94 and 78 ml/min/1.73m2, respectively (p < 0.001). (Fig. S2 in Supplementary materials).

Those findings were irrespective of cisplatin dose or the use of a bi-drug HIPEC regimen. The pairwise analysis did not show any difference between PHH + ST and ST alone groups.

3.4. Kidney failure rate analysis

Overall nephrological complications at 90-days rate was 10 % (n = 22/220), distributed in 20 % of PHH-group (n = 21/104), 3 % (n = 1/38) and 0 % in PHH + ST and ST, respectively (p < 0.001) (see Table 3).

We were further interested in the rates of acute and chronic renal injury. In PHH group, 20 % of patients (n = 21/104) developed postoperative acute kidney injury (AKI). Of these 21 patients, 18 % (n = 19/104) had developed chronic kidney disease (CKD, GFR <60 ml/min) at 3 months postoperatively, including 10/104 (10 %) stage IV CKD (GFR <30 ml/min). Three patients (3 %) required hemodialysis with one case (1 %) requiring renal transplantation. In PHH + ST group, we recorded one case (2.6 %) of AKI, secondary to severe sepsis without progression to CKD. Group with ST alone was uneventful (Fig. 2).

Table 1
Baseline characteristics.

Characteristic	Overall, N = 220[a]	PHH, N = 104[a]	PHH + ST, N = 38[a]	ST, N = 78[a]	p-value[b]
Age	59 (49, 68)	60 (48, 68)	60 (54, 69)	57 (49, 67)	0.8
Gender					<0.001
Female	168 (76 %)	89 (86 %)	31 (82 %)	48 (62 %)	
Male	52 (24 %)	15 (14 %)	7 (18 %)	30 (38 %)	
ASA					0.12
1	55 (25 %)	34 (33 %)	6 (16 %)	15 (19 %)	
2	137 (63 %)	59 (58 %)	25 (68 %)	53 (68 %)	
3	25 (12 %)	9 (8.8 %)	6 (16 %)	10 (13 %)	
Pathology					<0.001
ovarian	70 (32 %)	54 (52 %)	15 (39 %)	1 (1.3 %)	
colorectal	52 (24 %)	0 (0 %)	0 (0 %)	52 (67 %)	
gastric	38 (17 %)	11 (11 %)	11 (29 %)	16 (21 %)	
mesothelioma	27 (12 %)	22 (21 %)	4 (11 %)	1 (1.3 %)	
endometrial	9 (4.1 %)	6 (5.8 %)	3 (7.9 %)	0 (0 %)	
appendix	6 (2.7 %)	0 (0 %)	1 (2.6 %)	5 (6.4 %)	
pseudomyxoma	4 (1.8 %)	3 (2.9 %)	0 (0 %)	1 (1.3 %)	
other	14 (6.4 %)	8 (7.7 %)	4 (11 %)	2 (2.6 %)	

[a] Median (IQR); n (%).
[b] Kruskal-Wallis rank sum test: Pearson's Chi-squared test; Fisher's exact testPHH: peroperative hyperhydration group, ST: sodium-thiosulfate group.

Table 2
Surgical and pharmacologic data.

Characteristic	Overall, N = 220[a]	HS only, N = 104[a]	HS + ST, N = 38[a]	ST only, N = 78[a]	p-value[b]
PCI	9 (5, 14)	9 (5, 16)	9 (4, 15)	9 (6, 12)	0.6
CC-score					<0.001
CC-0	190 (87 %)	79 (77 %)	35 (92 %)	76 (97 %)	
CC-1	26 (12 %)	23 (22 %)	3 (7.9 %)	0 (0 %)	
CC-2	3 (1.4 %)	1 (1.0 %)	0 (0 %)	2 (2.6 %)	
HIPEC approach					>0.9
closed-abdomen	219 (100 %)	103 (99 %)	38 (100 %)	78 (100 %)	
open-abdomen	1 (0.5 %)	1 (1.0 %)	0 (0 %)	0 (0 %)	
HIPEC duration (min)					<0.001
60	106 (48 %)	85 (82 %)	20 (53 %)	1 (1.3 %)	
75	3 (1.4 %)	2 (1.9 %)	1 (2.6 %)	0 (0 %)	
80	2 (0.9 %)	1 (1.0 %)	1 (2.6 %)	0 (0 %)	
90	109 (50 %)	16 (15 %)	16 (42 %)	77 (99 %)	
HIPEC temperature (°C)					0.5
40	1 (0.5 %)	0 (0 %)	0 (0 %)	1 (1.3 %)	
42	219 (100 %)	104 (100 %)	38 (100 %)	77 (99 %)	
Drugs used for HIPEC					<0.001
cisplatin + doxorubicin	76 (35 %)	60 (58 %)	15 (39 %)	1 (1.3 %)	
cisplatin + mitomycin	6 (2.7 %)	2 (1.9 %)	0 (0 %)	4 (5.1 %)	
ciplatin only	138 (63 %)	42 (40 %)	23 (61 %)	73 (94 %)	
Cisplatin dose (mg/m^2)					<0.001
≤ 30	17 (10 %)	16 (25 %)	0 (0 %)	1 (1.6 %)	
50	64 (40 %)	39 (60 %)	21 (60 %)	4 (6.5 %)	
75	15 (9.3 %)	10 (15 %)	5 (14 %)	0 (0 %)	
100	66 (41 %)	0 (0 %)	9 (26 %)	57 (92 %)	
Doxorubicin dose (mg/m^2)					>0.9
15	53 (98 %)	38 (97 %)	14 (100 %)	1 (100 %)	
25	1 (1.9 %)	1 (2.6 %)	0 (0 %)	0 (0 %)	
Mitomycin dose (mg/m^2)					
15	2 (100 %)	0 (NA%)	0 (NA%)	2 (100 %)	

[a] Median (IQR); n (%).
[b] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test.

3.5. Other complications

The analysis of other postoperative complications is summarized in Table 3. We grouped the major complications into several categories and studied the major morbidity according to the Clavien classification. We found a significant difference concerning severe complications (Grade > II according to Clavien), with a rate of 60 %, 32 % and 54 %, in PHH, PHH + ST and ST group, (p = 0.014). The ST group exhibited a higher occurrence of septic complications (14 %, n = 11/78) in contrast to the PHH and PHH + ST groups, 8 % (n = 3/104) and 1 % (n = 1/38), respectively (p < 0.001).

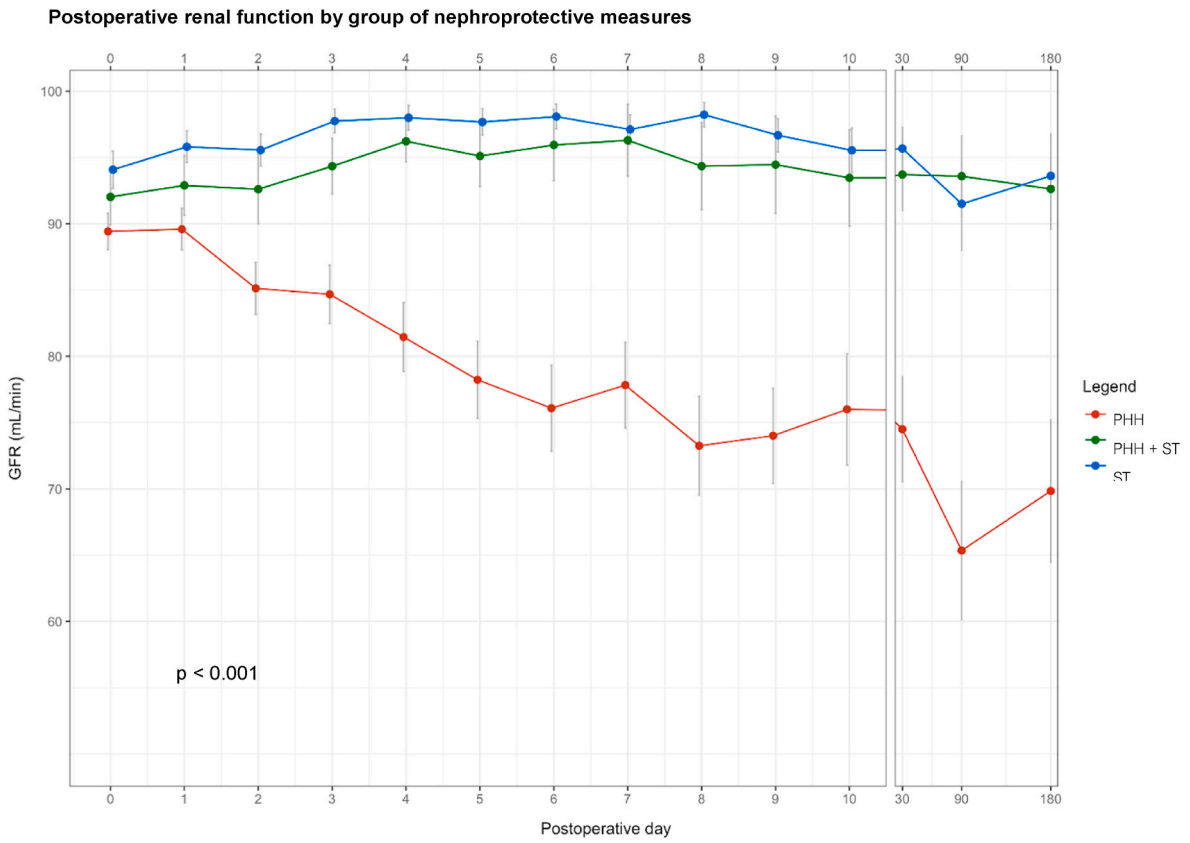

Fig. 1. Evolution of glomerular filtration rate.

Table 3
90-days postoperative complications.

Characteristic	Overall, N = 220[a]	PHH, N = 104[a]	PHH + ST, N = 38[a]	ST only, N = 78[a]	p-value[b]
Major morbidity (Dindo > II)	116 (53 %)	62 (60 %)	12 (32 %)	42 (54 %)	0.014
Hematologic complications	47 (21 %)	28 (27 %)	4 (11 %)	15 (19 %)	0.5
Cardiovascular complications	22 (10 %)	11 (11 %)	5 (13 %)	6 (8 %)	0.10
Septic complications	15 (7 %)	1 (1 %)	3 (8 %)	11 (14 %)	<0.001
Surgical complications	62 (28 %)	29 (28 %)	9 (24 %)	24 (31 %)	0.2
Gastro-intestinal complications	28 (13 %)	16 (15 %)	4 (11 %)	8 (10 %)	0.5
Respiratory complications	36 (16 %)	18 (17 %)	3 (8 %)	15 (19 %)	0.7
Nephrological complications	22 (10 %)	21 (20 %)	1 (3 %)	0 (0 %)	<0.001
Urinary complications	11 (5 %)	4 (4 %)	0 (0 %)	7 (9 %)	0.2
Mortality	2 (1 %)	1 (1 %)	0 (0 %)	1 (1 %)	>0.9

[a] n (%).
[b] Pearson's Chi-squared test; Fisher's exact testPHH: preoperative hyperhydration, ST: sodium thiosulfate.

4. Discussion

4.1. Summary of main results

This study provides important insights into the management of cisplatin-induced renal toxicity in patients undergoing cytoreductive surgery with HIPEC. The results of our study underlined that the use of ST can avoid the risk of renal insufficiency, even without the administration of PHH. No acute renal failure occurred in the group treated with ST alone whereas 20 % of patients presented with this complication in the group receiving PHH alone with 18 % of chronic renal failure. Cumulatively, we noted a higher incidence of septic complications in the sodium thiosulfate groups, PHH + ST and ST, at 8 % and 14 % respectively, in contrast to 1 % in the PHH group ($p < 0.001$).

4.2. Results in the context of published literature

These findings are significant as they add to the current body of knowledge on the prevention of cisplatin-induced renal damage. They have important clinical implications for the management of patients with ovarian cancer as HIPEC with cisplatin may be increasingly used since the positive results of several randomized trials evaluating HIPEC with cisplatin in first-line and recurrence settings [2,27–29]. Moreover, the reference treatment of peritoneal mesothelioma combines cytoreductive surgery with HIPEC using cisplatin in combination with doxorubicin [30]. And finally, HIPEC with cisplatin in combination with Mitomycin C could be used as a complementary curative or preventive treatment of some pseudomyxoma peritonei and peritoneal metastasis from gastric cancer [31,32]. In consequence, this finding may improve the preoperative management of many patients with peritoneal surface malignancies.

ST is a non-specific pharmacological agent used in many indications, including systemic adverse effects secondary to the use of platinum salts. In nephrology, its chelating action of cations made it used for the treatment of calciphylaxis occurring in patients under dialysis [33]. Historically, it has been used for the treatment of ringworm or as an antifungal agent. Its use is also described in the management of cyanide poisoning. It is a cation chelating agent. It has antioxidant properties related to its reaction with oxidized glutathione and reactive oxygen species leading to the formation of glutathione, a natural antioxidant. It

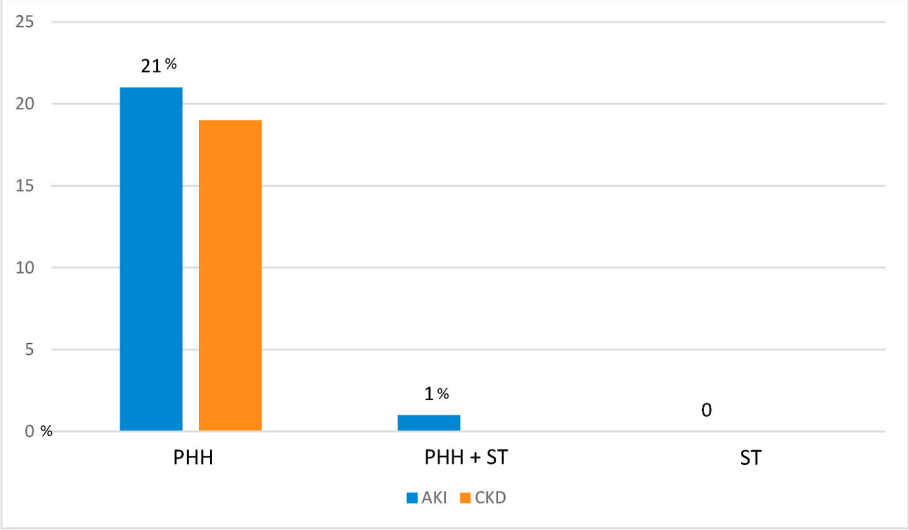

Fig. 2. 90-days post-operative renal failure percentage.
AKI: Acute renal insufficiency, CKI: Chronic renal insufficiency, PHH: preoperative, ST: sodium thiosulfate.

would thus restore the functions of endothelial cells. In addition, Sodium thiosulfate also interacts with various enzymes by transsulfurizations producing hydrogen sulphite, a vasodilator at the microcirculatory level. The plasma concentration of ST increases linearly with the injected dose [34]. The half-life of the plasma distribution phase is approximately 23 min. Regarding its elimination, some of the injected sodium thiosulfate is oxidized into sulfite and then into sulfate at the hepatic level. Only a small fraction of thiosulfate is incorporated into the endogenous sulfur compounds. Sodium thiosulfate is then mainly eliminated by the renal route, by glomerular filtration and secretion [19]. Sodium thiosulfate has anti-alkylating properties for which one could argue a potential inactivation or reduction of the efficiency of cisplatin. This phenomenon has previously been examined in a neuroblastoma model, revealing that the utilization of ST does not undermine the anti-tumor impact of CDDP, both within a controlled environment and within an animal representation [35,36]. However, its application in two substantial positive randomized trials showcasing the advantages of employing HIPEC with cisplatin presents the strongest counterargument [2,37]. Furthermore, in the CHIPOR trial, the introduction of ST was permitted after the study had commenced. Notably, the rate of renal failure stood at 10 % before its implementation, in contrast to the reduced rate of 3.9 % observed after its utilization [37].

The use of hyperhydration was established as an effective way of preventing renal failure. It is routinely used to ensure adequate diuresis and clearance during treatment with cisplatin. One of the proposed mechanisms is that forced diuresis enhances cisplatin excretion by enhancing renal blood flow and filtration and decreasing the contact time of cisplatin and renal tubules [14]. Moreover, one could hypothesize that hyperhydration can affect the central volume of distribution, decreasing cisplatin peak plasma concentrations. In a randomized trial, Santoso et al. compared hyperhydration alone to the administration of saline hydration combined with mannitol or furosemide and found that it was associated with a lower rate of renal failure secondary to cisplatin [38]. But hyperhydration in the context of cytoreductive surgery may also have potential inconveniences and risks: pulmonary edema, hyponatremia, increased risks of infection, bleeding, impaired wound healing, and anastomotic leaks [39–41].

We also investigated the rate of other postoperative complications, and we found a higher rate of septic complications in the ST group. This could be explained by the overrepresentation of colorectal cancers (67 % in the ST group compared to 0 % in the PHH group) and gastric cancers (29 % in the PHH + ST group compared to 11 % in the PHH group) in the group that received ST, leading to more intestinal anastomoses and a higher rate of complete cytoreductions (CC-0) in this group, resulting in more extensive surgeries and, consequently, more complications.

4.3. Strengths and weaknesses

Our study underscores the potential for streamlined patient care in the context of hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin through the use of sodium thiosulfate (ST). Despite the limitations of our retrospective analysis and the fact that we compared three successive periods with three populations not strictly comparable, our study supports the use of ST alone, without preoperative intravenous hyperhydration, as a way to limit the risk of volume overload, reduce length of stay, and decrease hospitalization costs. Additionally, it should be noted that while the technique (GFR based on creatinine) used for monitoring renal function is certainly the simplest, it may not be the most sensitive compared to other techniques (cystatin C, renal scintigraphy, biopsy) [42,43].

Furthermore, practices have evolved over the years with an improvement in perioperative management (ERAS, prehabilitation, continuous monitoring of cardiac and perioperative volume status), undoubtedly enhancing postoperative outcomes [44,45]. This is an additional argument to suggest that there should not be more complications in the group with ST, which is the most recent in terms of management. These aspects can be suggested due to the inability to collect data on perioperative management, which has certainly changed over the studied period.

4.4. Future research

These findings may prompt a reevaluation of existing preoperative hyperhydration protocols, aiming to optimize resource utilization while maintaining patient safety. Furthermore, the implementation of ST as a renoprotective strategy holds promise in enhancing both the safety and efficiency of cisplatin-based HIPEC procedures. The only way to provide a higher proof level would doubtless be proper to suggest a prospective randomized study but of poor interest.

4.5. Implications for practice

Although the management of renal toxicity caused by intraperitoneal cisplatin remains unclear, our study suggests that the exclusive use of

sodium thiosulfate, without the need for preoperative intravenous hyperhydration, may simplify perioperative care for complex patients without compromising safety.

5. Conclusion

Sodium thiosulfate alone effectively prevents renal toxicity in HIPEC-treated patients, making preoperative hyperhydration unnecessary.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript. All authors have no financial or personal relationships with individuals or organizations that could potentially bias or influence the research findings or the interpretation of the data presented in this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.107955.

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