International Journal of Surgery 64 (2019) 5–9

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Original Research

Postoperative hyperglycemia in patients undergoing cytoreductive surgery and HIPEC: A cohort study

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ARTICLE INFO

Keywords:
Hyperglycemia
Hyperthermic intraperitoneal chemotherapy
Peritoneal carcinomatosis

ABSTRACT

Background: Hyperglycemia following elective or emergency surgery is generally associated with an increased risk of complications. The impact of hyperglycemia following surgery for peritoneal surface malignancy remains unclear.

Materials and methods: Records of patients undergoing cytoreduction and HIPEC for peritoneal surface malignancy were reviewed at two institutions. Postoperative hyperglycemia was defined as serum glucose > 140 mg/dl at the first measurement after surgery. Lengths of stay and 30-day complication rates were recorded.

Results: There were 115 total patients included, 65 from Institution A (A) and 50 from Institution B (B). Perioperative steroids were given to 55% (A) and 100% (B) of patients, with postoperative hyperglycemia present in 39% and 86% of patients respectively. Complication rates were not significantly different in patients with hyperglycemia versus patients who were normoglycemic at each site [56% vs. 53%, $p = 0.8$ at (A); 47% vs. 43%, $p = 1.0$ at (B)]. Infection rates were also similar between groups [16% vs. 13%, $p = 0.72$ at (A); 14% vs. 29%, $p = 0.31$ at (B)].

Conclusions: Rates of hyperglycemia in patients undergoing cytoreduction and HIPEC are high. This likely represents a stress response but does not seem to have the same adverse impact as seen in other abdominal surgical patient populations.

1. Introduction

The treatment modality of cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) is gaining acceptance as a treatment for patients with peritoneal surface disease. Cytoreductive surgery and HIPEC as described by Dr. Sugarbaker and others has prolonged survival for these patients but has a high complication rate of 40–60% [1–4] and a median length of stay of 9–15 days [1,3–8]. Perioperative hyperglycemia has been studied in multiple patient populations including organ transplantations, cardiac, colorectal and elective general surgery [9–14]. In all of these studies, hyperglycemia has been associated with an increased rate of complications, including increased infectious complications and increased length of stay. Intensive insulin therapy was shown to improve outcomes in surgical intensive care patients [14], prompting evaluation of glycemic control in other surgical patient populations. Aggressive glycemic control places patients at risk of hypoglycemia, however, which has also been associated with adverse outcomes [15].

The impact of postoperative hyperglycemia in patients with peritoneal surface disease has not been studied. This is a complicated group of patients who often have been treated with many cycles of chemotherapy, by definition have advanced malignancy, and who undergo a long operative procedure of cytoreduction and heated intraperitoneal chemotherapy. In an effort to improve outcomes and decrease complications in this patient population, we looked at the effect of postoperative hyperglycemia in patients undergoing cytoreductive surgery as a target for possible intervention. An additional goal was to understand the clinical impact of perioperative use of corticosteroids, which are often utilized in the perioperative period for reducing nausea but at the risk of inducing hyperglycemia.

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https://doi.org/10.1016/j.ijsu.2019.02.005
Received 19 November 2018; Received in revised form 27 December 2018; Accepted 6 February 2019
Available online 15 February 2019
1743-9191/

2. Methods

2.1. Patient selection

We retrospectively evaluated all patients with peritoneal surface disease of any histology including but not limited to colon, appendix, mesothelium, gastric or biliary tumors who have undergone exploratory laparotomy with the intention of performing cytoreductive surgery and heated intraperitoneal chemotherapy. Outcomes were not separately analyzed by histology. The patients were treated at two different institutions, Institution A and Institution B, from 2004 through August 2015. The institutional review boards of both institutions approved this study. The work has been reported in line with the STROCSS criteria [16].

Data collected on each patient includes age, preoperative, intraoperative and maximum serum glucose levels in the first 24 h after surgery, perioperative steroid use, the peritoneal cancer index, completeness of cytoreduction, insulin use, history of diabetes and time to recurrence. The peritoneal cancer index (PCI) was calculated in each case as described by Jacquet and Sugarbaker. PCI includes 13 abdominal regions with each region graded on a scale of 0–3 based on the amount of tumor present at each location (0 = no tumor, 1 = tumor up to 0.5 cm, 2 = tumor up to 5.0 cm, 3 = tumor greater than 5.0 cm or confluence) to a computed index ranging from 0 to 39 [17]. Residual disease following cytoreductive surgery was scored according to the completeness of cytoreduction (CC) score as described by Sugarbaker [17]. A CC of 0 or 1 are considered complete cytoreduction with no visible nodules or nodules < 0.25 cm, respectively. CC2 indicates moderate residual disease with nodules between ≥0.25 cm and ≤2.5 cm, and CC3 indicates gross residual disease with nodules > 2.5 cm. Hyperglycemia was defined as serum glucose > 140 mg/dl at the first post-operative measurement. The first postoperative measurement is obtained upon arrival to the postoperative recovery unit.

The primary endpoints were infectious complications and overall complications within 30 days of surgery, and length of stay. Secondary endpoints included completeness of cytoreduction, peritoneal cancer index and time to recurrence.

2.2. Statistical analysis

The primary statistical goal was to compare patients with and without hyperglycemia. Fisher's Exact test was used for categorical outcomes and the Wilcoxon rank-sum test was used for continuous outcomes. Kaplan-Meier curves [18] were used for time to recurrence. Overall survival was not analyzed because there were too few events for meaningful statistical analysis. Statistical analysis was conducted separately by institution, unless otherwise noted.

3. Results

A total of 115 patients were treated with cytoreductive surgery and HIPEC from 2004 through 2015 at the two institutions, with 50 patients (43%) treated at Institution B (B) and 65 patients (57%) treated at Institution A (A). Patient characteristics stratified by institution are summarized in Table 1. Only 4% (A) and 6% (B) of patients had underlying diabetes. Statistical analysis was performed including and excluding these patients, with no qualitative difference in results. The results reported below include these patients. The majority of the patients from (A) underwent treatment for adenocarcinomas of gastrointestinal origins and received mitomycin C in plasmalyte (97%), while the majority of the patients from (B) had either mesothelioma and received cisplatin in Ringer's lactate (76%) or gastrointestinal malignancies and received mitomycin C (24%) in Ringer's lactate. Hyperglycemia occurred in 39% of (A) patients and 86% of (B) patients.

Patient outcomes by hyperglycemia are summarized for each institution in Table 2. Rates of infectious complications [14% at (A) and 16% at (B)] and overall complications [54% at (A) and 46% at (B)] were similar at each institution, with no significant differences by hyperglycemia status at either institution. Infectious complications at A were most commonly wound infections or urinary tract infection, with one anastomotic leak and one intra-abdominal abscess. Infectious complications at B were also most commonly wound infections, and one case of *C. difficile* colitis. Non-infectious complications at both A and B included ileus and anemia, with patients at B also having acute renal failure that usually resolved without dialysis, or pulmonary embolism. Median lengths of stay were 8 and 10 days at (A) and (B) respectively, with no significant differences by hyperglycemia status. PCI and completeness of cytoreduction were similar between Institution A and B, and were not significantly different between hyperglycemic and normoglycemic patients in either institution (p = NS).

Table 1
Patient characteristics.

	Institution A (n = 65)	Institution B (n = 50)	p value
Age			0.11
Mean (SD)	56.5 (11.9)	59.2 (13.3)	
Median	58	63	
Range	(20–82)	(19–78)	
Diabetes mellitus	4 (6%)	2 (4%)	0.93
CC			< 0.001
0	39 (60%)	16 (32%)	
1	9 (14%)	25 (50%)	
2	7 (11%)	5 (10%)	
3	10 (15%)	4 (8%)	
PCI			0.21
N	62	50	
Mean (SD)	14.7 (10.5)	15.9 (7.7)	
Median	13	15	
Range	(1-39)	(0-33)	
Diagnosis			< 0.001
Adenocarcinoma (colon or appendix)	42 65%)	12 (24%)	
Mucinous appendiceal neoplasm	9 (14%)	0 (0%)	
Mesothelioma	0 (0%)	38 (76%)	
Other	14 (22%)	0 (0%)	
Perioperative steroids			< 0.001
No	29 (45%)	0 (0%)	
Yes	36 (55%)	50 (100%)	
Hyperglycemia			
First post-operative glucose	25 (39%)	43 (86%)	< 0.001
Mean (SD)	135.5 (37.0)	199.5 (49.5)	
Median	130	194	
Range	(72–233)	(117–289)	
During first 24 h post-op	34 (52%)	45 (90%)	< 0.001
Mean (SD)	140.2 (37.2)	213.6 (51.1)	
Median	141	207	
Range	(73–233)	(121–308)	

Steroids (dexamethasone 10 mg-20 mg) were given intraoperatively to reduce postoperative nausea and vomiting in all patients at (B). At (A), 36 (55%) patients received preoperative dexamethasone (4 mg-8mg), with 16 of 36 (44%) having hyperglycemia. Rates of hyperglycemia were not significantly different in those patients who did not receive steroids, 9 of 29 (31%) patients (p = 0.31) at (A). At (A), rates of complications by steroid use were similar and non-significant. Infectious complications occurred in 14% in each steroid group (p = 0.99) and any complications occurred in 58% of patients with steroids and 48% with no steroids (p = 0.42).

We analyzed the impact of insulin used to treat postoperative hyperglycemia. At (A), 25 patients had hyperglycemia at their first postoperative glucose check, with 17 (68%) receiving insulin. In the (B) cohort, of the 43 patients who were hyperglycemic, only 10 patients (26%) received insulin. Insulin was administered per the discretion of the managing team at each institution. For both cohorts, no significant differences were found for infectious complications, any complication

Table 2
Outcomes.

	Institution A			Institution B		
	No Hyperglycemia	Hyperglycemia	p value	No Hyperglycemia	Hyperglycemia	p value
	(n = 40)	(n = 25)		(n = 7)	(n = 43)	
All complications	21 (53%)	14 (56%)	0.80	3 (43%)	20 (47%)	1.00
Infection	5 (13%)	4 (16%)	0.72	2 (29%)	6 (14%)	0.31
Non-infectious complications	16 (40%)	10 (40%)	1.0	1 (14%)	14 (33%)	0.66
Length of stay			0.92			0.75
Mean (SD)	9.3 (4.3)	9.2 (4.1)		12.7 (6.8)	10.9 (2.9)	
Median	9	8		10	10	
Range	(3-23)	(5-26)		(7-27)	(6-18)	
CC			0.08			1.00
CC 0-2	31 (78%)	24 (96%)		7 (100%)	39 (91%)	
CC 3	9 (23%)	1 (4%)		0 (0%)	4 (9%)	
PCI			0.37			0.73
N	37	25		7	43	
Mean (SD)	15.9 (11.2)	13.0 (9.3)		13.9 (7.9)	16.3 (7.7)	
Median	14	9		17	14	
Range	(1-39)	(1-32)		(0-22)	(2-33)	

or length of stay between the patients who received insulin and those who did not.

We examined the relationship between completeness of cytoreduction, PCI and hyperglycemia. Only 7 patients at (B) were normoglycemic, so only the (A) population was analyzed. Patients with a CC0-1 were more likely to have hyperglycemia, 44% (21 of 48 patients), compared to 23% (4 of 17 patients) with a CC2-3, but this was not statistically significant ($p = 0.16$). PCI did not significantly differ by hyperglycemia status, with a median of 9 in hyperglycemic patients and 14 in normoglycemic patients, $p = 0.37$.

For patients with a completeness of cytoreduction score of CC0 or CC1, Fig. 1 shows Kaplan-Meier estimates of time to recurrence by hyperglycemia status, separately for each institution. For (A), those with hyperglycemia had a shorter time to recurrence, but differences were not significant among all groups ($p = 0.53$). In the (B) cohort, only 6 patients had no hyperglycemia, and thus no estimate was produced for this group.

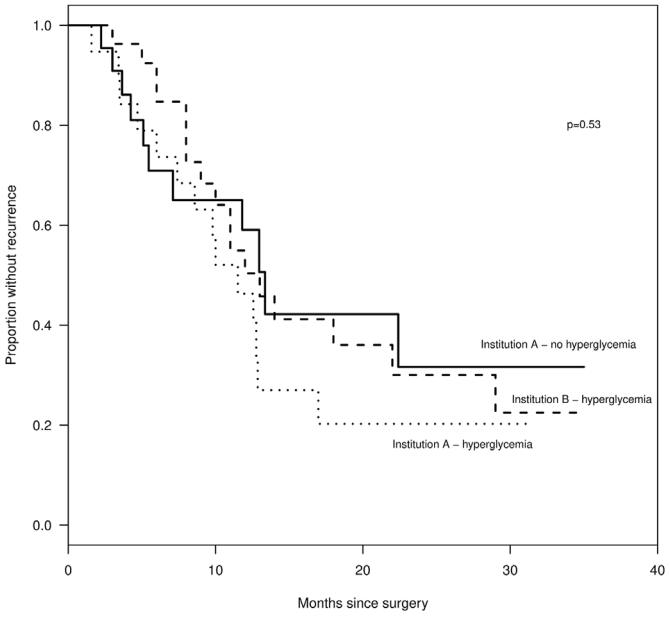

Fig. 1. Kaplan-Meier curves of time to recurrence by hyperglycemia status among patients with CC = 0 or 1 at each site (Institution A; Institution B). Institution B with no hyperglycemia was not estimated because only 6 patients were included in that group.

4. Discussion

Patients with advanced malignancy who are treated with cytoreduction and HIPEC have a high rate of postoperative complication, which may affect their long term oncologic outcome [19]. We assessed the impact of postoperative hyperglycemia on outcome in this patient population, as a possible target for intervention. We studied patients at two institutions undergoing similar operations, with somewhat different diseases and perioperative protocols. This allows us to assess the impact of differences in protocol. The majority of patients undergoing cytoreductive surgery and HIPEC did develop hyperglycemia postoperatively but this did not impact patient outcome. Hyperglycemia in this patient population can be precipitated by perfusion with dialysate solutions, which contain 1.5% dextrose, or oxaliplatin, which is delivered in 5% dextrose in water (D5W). Intraoperative hyperglycemia was recently reviewed [19] and while sometimes severe, also was not associated with adverse outcomes such as increased length of stay or infectious complications. In our institutions, we use a glucose free perfusate, which eliminates this factor as a cause of perioperative hyperglycemia.

A hypermetabolic stress response characterized by hyperglycemia and insulin resistance is common after major trauma or surgery [15]. This response was initially thought to be beneficial, as an additional glucose supply is available for energy. Evidence then accumulated that severe acute hyperglycemia causes several adverse effects, particularly on monocyte and neutrophil function and blood coagulation. Insulin therapy was used in critically ill patients, and early improvements in outcome led to formal trials [14]. Van den Berghe et al. [14] demonstrated that intensive insulin therapy improved outcomes in surgical intensive care, with reduced morbidity and mortality. In this early randomized trial, subjects in the intensive insulin group had a target glucose range of 80–110 mg/dl. They found a significant reduction in bloodstream infections, acute renal failure, and number of days of mechanical ventilation. Based on these results, stress hyperglycemia in postoperative patients has been targeted as a possible intervention to improve patient outcomes in a non-ICU setting.

In patients undergoing a variety of major operative procedures, hyperglycemia has been shown to be associated with several adverse outcomes. Postoperative hyperglycemia was found to be associated with increased surgical site infections in patients undergoing ventral hernia repair [11], mastectomy [12], and colectomy [13,20], and increased infectious complications in pancreatoduodenectomy [21,22]. Hyperglycemia has also been linked to increased length of stay with ventral hernia repair [11] and the need for repeat laparotomy in

pancreatoduodenectomy [22]. In contrast to these findings, recently presented work has shown that in patients with bladder cancer undergoing radical cystectomy, postoperative hyperglycemia was associated with lower hospital length of stay and cost (Linskey et al. Academic Surgical Congress, February 2017). Furthermore, the initial findings of van den Berghe have not been confirmed, and several trials have not found a benefit to strict glycemic control [15]. This is consistent with what we have found in the HIPEC patient population where early postoperative hyperglycemia does not predict adverse outcomes or increased length of stay. More recent findings point to glucose variability as a predictor of poor outcome, although we did not explore that parameter in this study.

The use of perioperative steroids does appear to make hyperglycemia more likely, with higher rates of hyperglycemia seen in the (B) cohort of patients who all received high dose dexamethasone intraoperatively. This increased rate of hyperglycemia did not have an effect on the number of infectious complications, the number of any complication, or the length of stay. With lower doses of dexamethasone used in the (A) population there was no effect on blood glucose levels.

The lower dose and rate of steroids used in the (A) cohort allows us to look for a relationship between the level of hyperglycemia and the completeness of cytoreduction. Patients who were unable to undergo complete cytoreduction, with CC values of 2–3 were less likely to mount a hyperglycemic response to the stress of surgery. This lack of response to surgical stress may be an indicator of poor prognosis in patients with a high burden of disease. The use of high dose dexamethasone in the (B) group may obscure the lack of a stress response in the setting of a high burden of disease. An alternative explanation is that the lack of hyperglycemia reflects a shorter operative time and less dissection. This finding should be explored in a larger group of patients who did not receive high dose steroids.

In this small population of patients, there was no significant long-term consequence of hyperglycemia. The difference in rates of recurrence seen in the (B) patients compared to the (A) patients is likely due to differences in histology. Survival was not analyzed due to the low number of events. The effect of hyperglycemia on the efficacy of chemotherapy has not been studied extensively, and the long term impact of hyperglycemia and/or diabetes on cancer outcomes is difficult to discern. Multiple clinical studies have shown an increased all-cause mortality rate in cancer patients with diabetes compared to patients without diabetes, as well as an increased rate of complications from chemotherapy [23–27]. This may well be related to poor outcomes associated with the diabetes alone, or due to diabetic patients receiving less aggressive treatment [24]. A recent review examined preclinical studies which have showed mixed results in the effect of hyperglycemia on the efficacy of chemotherapy in cell culture [27]. Many studies find reduced response to chemotherapy in a hyperglycemic environment, but other studies find no difference or even potentiation of chemotherapy effect with hyperglycemia. Further exploration of the effect of hyperglycemia on the efficacy of HIPEC is necessary.

The variety of patients and perioperative protocols in this study population did allow us to assess the impact of perioperative steroids and insulin on rates of hyperglycemia and outcomes, but also creates the limitation of small numbers in any given group. Patients included in this study had tumors ranging from low grade mucinous appendiceal neoplasms to high grade colorectal cancer, endometrial cancer or gastric cancer. The relationship of tumor histology to metabolic stress from surgery is unknown, and may warrant exploration in a larger study.

5. Conclusion

The rate of hyperglycemia in patients undergoing cytoreductive surgery and HIPEC is high but this does not seem to have the adverse impact on complication rate or length of stay as seen in other surgical patient populations. There may be an association between lack of hyperglycemia and advanced disease, but this is a small retrospective study and results need to be verified with a larger cohort of patients. In terms of reducing complication rates, control of blood glucose levels postoperatively has no significant short-term effect and further investigation into other targets for intervention are needed.

Ethical approval

IRB approval was granted by Penn State Milton S. Hershey Medical Center, Hershey,Pennsylvania and Moffitt Cancer Center, Tampa, Florida, from 2004 through August 2018. The institutional review boards of both institutions approved this study. Reference number 1916.

Sources of funding

None.

Author contribution

Study concept and design: Pameijer, Soybel.
Acquisition and analysis of data: DiSano, Wischhusen, Schaefer.
Interpretation of data: Pameijer, Wong, Dessureault, Soybel.
Drafting of the manuscript: DiSano.
Critical revision of the manuscript for important intellectual content: Pameijer.
Soybel, Dessureault.
Study supervision: Pameijer.

Conflicts of interest

None of the authors have any conflicts of interest.

Research registry number

researchregistry4263.

Guarantor

Colette Pameijer.

Data statement

The data will be made available upon request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

Julie A. DiSano: Conceptualization, Methodology, Data curation, Investigation, Writing - original draft. **Jonathan Wischhusen:** Data curation. **Eric W. Schaefer:** Formal analysis, Visualization, Investigation. **Sophie Dessureault:** Supervision, Writing - review & editing. **Joyce Wong:** Conceptualization, Resources. **David I. Soybel:** Writing - review & editing, Supervision. **Colette R. Pameijer:** Supervision, Conceptualization, Validation, Project administration, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.02.005.

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