The use of Hypotension Prediction Index in cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)

INTRODUCTION

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is a complex surgical procedure with significant complications. These complications stem from extremes of haemodynamics, biochemical abnormalities and thermal fluctuations that the patient is subjected to, with morbidity and mortality rates going up to 20%–40% and 3%, respectively.[1,2] Cardiac output monitoring is being used during CRS-HIPEC in many centres, for patients with high-volume disease.[2] Goal-directed therapy in CRS-HIPEC has been shown to lower morbidity. The HemoSphere advanced monitoring platform along with the Acumen sensor (Edwards Lifesciences, Irvine, CA), is equipped with additional parameters to allow clinicians to pre-emptively recognise and treat impending hypotension.[3] The Hypotension Prediction Index (HPI), is based on arterial waveform features and predicts the occurrence of hypotension (defined as mean arterial pressure (MAP) less than 65 mmHg for at least 1 minute).[4] HPI is displayed as a unit less number from 0-100, with higher values being inversely proportional to the time to impending hypotension. An HPI of 85 implies that there is an 85% probability of a hypotensive event in the next 15 minutes.[4] A high HPI value increases the certainty of hypotension (MAP <65 mmHg). Other derived parameters such as dP/dt_{max}, which is the maximal change in the left ventricular pressure over time, and dynamic arterial elastance (Ea_{dyn}), which is the ratio of pulse pressure variation (PPV) and stroke volume variation (SVV), which help determine fluid responsiveness, myocardial contractility and determine whether fluid bolus will increase the MAP.[3]

HPI has been used successfully in cardiac and thoracic surgeries but there is no literature on its efficacy in CRS-HIPEC surgeries, which involves massive blood loss, major fluid shifts, haemodynamic alterations and require a large volume of fluids. This article details the use of HPI in the prevention and treatment of hypotensive episodes in four patients undergoing CRS-HIPEC. Written informed consent has been obtained from all the patients for publication of the data.

CASES

The demographic details and surgical characteristics of the patients were obtained and entered [Table 1]. The standard anaesthesia protocol for patients undergoing CRS-HIPEC included general anaesthesia using inhalational anaesthetics and non-depolarising muscle relaxants, invasive blood pressure monitoring using radial arterial line and central venous access via the internal jugular vein. Our institutional protocol for haemodynamic monitoring in these patients included the use of arterial pressure-based cardiac output monitoring. The Edwards Lifesciences HemoSphere Advanced monitoring system with the Acumen sensor was used for the first time in patients undergoing CRS-HIPEC in our institute.

We recorded 12 instances of clinically significant instances of hypotension, where HPI values were higher than 85 and intervention was made by the anaesthesiologist based on these values. Data regarding the duration of hypotension, other haemodynamic parameters, the presumed causes of hypotension and the measures taken for correction were also obtained [Table 2].

Complete cytoreduction was achieved in all patients, and they received combination chemotherapy with doxorubicin and mitomycin-C. The duration of HIPEC was 60-90 minutes, while the surgery lasted between 585-780 minutes. All four patients required vasopressor support (injection noradrenaline) during the surgery, ranging from 0.1-0.3 µg/kg/min but the support was tapered off in three of them by the end of surgery. One patient continued to require 0.2 µg/kg/min, at the end of the surgery, which was tapered off 3 hours after surgery. All the patients were sedated and ventilated overnight in the intensive care unit. The purview of our case series is limited to the intra-operative period. Since the purpose of the case series was to evaluate the utility of this novel technology and to assess the possibilities of the monitor in predicting the relevant clinical responses to be followed in HIPEC surgeries, the values were noted and clinical decisions were made at the discretion of the anaesthesiologists.

Table 1: Demographic parameters and surgical characteristics

Patient	Age (years)/Gender	ASA	Primary Disease/Organ	PCI	CRS Excision	HIPEC drugs	HIPEC Duration	Blood Loss (ml)	Urine Output (ml)	Fluids (ml)	Duration of Surgery (min)	Vasopressor support at end of surgery (µg/kg/min)
Patient 1	69/M	II (IHD)	Appendix	20	Total Peritonectomy + greater and lesser omentectomy + small Bowel resection anastomosis + Retroperitoneal deposit excision + bilateral Diaphragmatic peritonectomy + Cholecystectomy + Port site excision)	Mitomycin + Doxorubicin 15 mg/m^2	60	2000	1500	RL 4500 Albumin 4% 1500 PRBC 256	675	0
Patient 2	35/F	II (Current Hypothyroidism)	Krukenberg's tumour secondary to metastatic adenocarcinoma of colon	7	Anterolateral parietal peritonectomy, pelvic peritonectomy, TAH, BSO, Redo low anterior resection, Small bowel RA, Omentectomy, Hartmann colostomy.	Mitomycin + Doxorubicin 15 mg/m^2	90	3400	1750	RL 6000 Albumin 4% 500 Gelofusine 500 PRBC 765	675	0
Patient 3	45/F	I	Appendix	34	Total peritonectomy + anterior resection + limited right hemicolecomy + splenectomy + omentectomy + cholecystectomy + falciform ligament excision + glisson capsule excision	Mitomycin + Doxorubicin 15 mg/m^2	90	3200	1900	RL 10000 Gelofusine 2500 Albumin4% 1000 PRBC 760 FFP 410	780	0.2
Patient 4	49/F	I	Adnexal mass with pseudomyxoma peritonei	10	Total parietal peritonectomy + Omentectomy (Operated for CRS-HIPEC in 2019)	Mitomycin + Doxorubicin 15 mg/m^2	60	3500	2100	RL 7000 Albumin 4% 1500 PRBC 780 FFP 650	585	0

ASA: American Society of Anesthesiologists; CRS: Cytoreductive Surgery; FFP: Fresh Frozen Plasma; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; PRBC: Packed Red Blood Cells; PCI: Peritoneal Carcinomatosis Index; RL: Ringer Lactate; TAH-BSO: Total Abdominal Hysterectomy-Bilateral Salpingooophorectomy; M-male; F-female; IHD- Ischaemic heart disease, RA: Resection-anastomosis

Patient	Instances where HPI >85	Phase of surgery	HPI	MAP	SVI	PPV	SVV	Ea$_{Dyn}$	dP/dt	Determined cause of hypotension	Intervention
										Table 2: Incidences of clinically significant HPI with interventions carried out	
Patient 1	2	CRS	96	69	31	21	22	1.1	450	No clinical hypotension seen but ooze from gall bladder fossa noticed	Bleeder coagulated by the surgeons
		CRS	100	60	24	30	31	1.1	357	Surgical compression on the IVC	200 ml crystalloid bolus, recovery soon after release of compression
Patient 2	2	CRS	96	65	28	47	40	1.2	504	Bleeding during adhesiolysis between the uterus and bladder	200 mL crystalloid bolus given
		CRS	100	63	34	38	28	1.4	500	Inferior vena cava compression	Recovery after the retraction was released
Patient 3	4	CRS	100	61	37	40	27	1.5	499	Liver retraction during diaphragmatic stripping	Normal values after retraction released
		CRS	100	57	42	42	28	1.5	524	Accidental surgical nick in the inferior mesenteric artery	Fluid bolus given, surgical control achieved
		CRS	100	63	49	16	14	1.1	868	Mean arterial pressures below 65 mm of Hg but above 60 mm of Hg	No action taken
		HIPEC	96	67	53	6	8	0.7	632	Vasodilatation after start of HIPEC phase	Noradrenaline infusion started in addition to increasing the rate of fluid administration
Patient 4	4	CRS	96	67	40	12	13	1	560	Blood loss of 1000 ml	500 ml of colloid bolus and Noradrenaline infusion started
		CRS	95	65	38	16	14	1.1	565	IVC compression by the surgeons	No active intervention, value normalised on release of compression
		CRS	97	63	29	46	34	1.3	522	Ongoing loss 2500 mL	Crystalloid bolus of 500 mL and colloid bolus of 250 ml
		CRS	86	68	42	10	9	1.1	898	Sudden loss of 600 mL	Colloid bolus 500 mL, increased rate of Noradrenaline infusion

CRS: Cytoreductive Surgery; HIPEC: Hyperthemic Intraperitoneal Chemotherapy; HPI: Hypotension Prediction Index; IVC: Inferior Vena Cava; MAP: Mean Arterial Pressure; PPV: Pulse Pressure Variation; SVI: Stroke Volume Index; SVV: Stroke Volume Variation

DISCUSSION

CRS-HIPEC has become the standard of care for peritoneal malignancies. Both the CRS and HIPEC phases have diverse surgical demands which can be a challenge for anaesthesiologists. During the CRS phase, extensive resection and exposure of large areas of raw peritoneum leads to major blood loss, massive fluid shifts and a propensity for hypothermia. During the HIPEC phase, exposure to hyperthermia leads to hyperdynamic perfusion and coagulation abnormalities, and exposure to toxic chemotherapeutic agents can lead to nephrotoxicity, cardiotoxicity, dyselectrolytemia and metabolic acidosis.[1,2,5]

During the CRS phase alone, the fluid losses may reach as high as 8-12 ml/kg.[2] Overestimating fluid requirements can cause increased morbidity from abdominal, cardiac and pulmonary complications, while underestimating the requirements can lead to inadequate tissue and renal perfusion.

There is evidence to suggest that sustained intra-operative hypotension (IOH) can lead to complications such as acute kidney injury, myocardial injury, and cerebrovascular accident, when the MAP falls <80 mmHg for ≥10 minutes or to <70 mmHg for even smaller durations.[6] In order to aid decision making when the HPI value is high, HemoSphere provides a 'decision tree' consisting of three other variables i.e., SVV or PPV, dP/dt$_{max}$ and Ea$_{dyn}$. dP/dt$_{max}$ is the maximal change in the left ventricular pressure over time. It is a surrogate measure of the contractility of the left ventricle, which is derived from the steepness of the upslope or the systolic part of the arterial waveform.[7] Since HPI predicts the occurrence of hypotension, it may facilitate pre-emptive action and prevent the hypotension from occurring. The Hypotension Prediction (HYPE) trial found that the use of a machine derived early warning system allowed faster responses leading to significantly shorter durations of hypotension (8.0 minutes versus 32.7 minutes, $P < 0.001$).[8] Various studies document the successful use of HPI in cardiac and non-cardiac surgeries.[9-12]

Ea$_{dyn}$ is calculated as an average of three consecutive measurements of the SVV and PPV at a specific time

point.[13] Values of Ea_{dyn} above 0.73 at the time of the hypotensive episode suggest fluid responsiveness.[14] Thus, the analysis of HPI in conjunction with the concurrent values of SPV or PPV, dP/dt_{max} and Ea_{dyn}, can guide the fluid therapy, vasopressor and inotrope administration in a hypotensive patient.

Of all the incidences with high HPI values, three could be attributed to bleeding [Table 2]. The increase in HPI served as a forewarning and enabled us to alert the surgeon to a concealed source of bleeding on two of these occasions. Since the resultant hypovolaemia presented with a concurrent increase in values, fluid boluses were used in treating the hypotension. The three incidents described above occurred in the CRS phase. However, one episode of hypotension, which occurred in the HIPEC phase, was seen to be associated with high HPI values but low Ea_{dyn} values. This helped us initiate vasopressor support in the form of injection of noradrenaline to augment MAPs, which led to its rapid correction.

A key drawback of the existent HPI algorithm is that the values are computed for a MAP of 65. While there is no standard definition of IOH, an absolute systolic pressure less than 100 mmHg with or without a relative decrease of 30% from baseline, is usually used to clinically identify IOH.[12] Given the accepted working definition, a MAP up to 60 mmHg would be acceptable in normotensive patients while known hypertensive patients may require a higher MAP for organ perfusion.[15] As a result, the software would be rendered incapable of accurately predicting hypotensive episodes in a significant proportion of the patient population.

Since HPI is calculated using the analysis of the arterial waveform, it could be influenced by factors such as the location of the arterial cannula and factors which could cause variable cardiac output such as atrial fibrillation and surgical retraction leading to compression of the inferior vena cava with a subsequent transient decrease in cardiac output.[5] On three separate occasions, the authors found raised HPI values, due to surgical retraction. The timing of these instances, proposed causes and interventions implemented were variable [Table 2]. Our findings suggest that, although the HPI values aid in decision-making, hypotension caused by acute changes can lead to simultaneous sharp increases in HPI values which could possibly be a reflection of the hypotension itself. Any planned action must take into account, not only the available

haemodynamic parameters including HPI but also the surgical intervention at that time which can cause acute changes in the values, precluding prediction. Literature suggests that, in patients with high volume disease, where the surgical duration exceeds 12 hours, fluid shifts are likely to require transfusion of more than 3-4 times the circulating volume and can predispose the patients to various complications including cardiac arrest.[1] In such patients, HPI is likely to be invaluable in administering the correct amount of fluid and prevent hypotension.

CONCLUSION

The incorporation of HPI increases the margin of safety in patients undergoing major surgical procedures with large fluid shifts and wide haemodynamic fluctuations. The current HPI technology has its own limitations, thus limiting the number of patients and circumstances in which hypotension can be predicted reliably. In conjunction with other clinical and haemodynamic parameters, HPI can unquestionably enhance postoperative outcomes.

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