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ORIGINAL ARTICLE

Are you in a poor country; hyper-thermic intra-peritoneal chemotherapy is still in reach: A clinical trial.

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ABSTRACT

Background: hyper-thermic intra-peritoneal chemotherapy (HIPEC) is established now as a considerably effective treatment method for peritoneal surface malignancy after optimal cyto-reduction. The obstacle faced by poor places is the high cost of the standard machines and their consumable kit per procedure. This opened the door for the trials of innovating cheaper ones as the one we deigned.

Methods: We evaluated the cost of the machine of our design, its expenses per procedure as well as the success of achieving the target temperature and good flow rate, safety aspects, technical failures and the technical support required. The comparison with standard machines was based on the manufacturer information and published reports and not on personal use.

Results: Form 2014 to 2017; we performed HIPEC (Coliseum technique) for patients using the machine of our design. Flow rate was 2 L/min and target temperature between 41 and 43 °C could be achieved in all cases. There were no technical failures and there was no safety issue recorded. Chemotherapy costs were not included and independent from the devices used. Cost of consumable kit was 110 USD/procedure, as compared to 1800 to 3500 USD/procedure for commercially available products. The cost for standard machines is between 40,000 and 135,000 USD.

Conclusions: Our design in HIPEC machine was efficient, easy to use, with no recorded complications from technical accidents or failure.

Key words: HIPEC, newly designed machine, standard machine

INTRODUCTION

Peritoneal carcinomatosis (PC) is a well-known sequel of multiple abdominal malignancies either arising from the gastro-intestinal tract or of gynaecologic origin. On occurrence, PC is mostly considered as a very bad prognostic sign hence it affects the overall survival with very poor response to systemic chemotherapy. [(1)]

PC sometimes represents the only form of recurrence in cases with recurrent gastric (50%), colonic (10-35%) or ovarian cancer. While in 15% of colonic cancer and 40% of gastric cancer and most cases of ovarian cancer, PC is found on abdominal exploration on the 1st presentation. [(1)]

In addition to PC, peritoneal mesothelioma, primary peritoneal carcinoma and pseudo-myxoma peritonii represent a challenging form of tumours affecting the peritoneal cavity. [(2)]

On introduction of the new concept of combined optimal cyto-reduction (CRS) followed by hyper-thermic intra-peritoneal chemotherapy (HIPEC), promising prognosis began to be shown. [(3)]

The HIPEC step involves irrigation of the abdominal cavity after the cyto-reduction step with chemotherapy (which consists of a specific chemotherapy drug according to the pathology of the tumour dissolved in one of multiple perfusates) heated to 41°-43° for an average of 90 minutes. This irrigation can be done while the abdomen is still open (open method) or temporarily closed (closed), in either of which a well-known HIPEC machine is used. [(4)]

A major obstacle which may face application of HIPEC manoeuvre is the cost either of the machine or the disposable kit used in handling the chemotherapy, heating it and delivering it to the patient, hence we established our machine design with its disposable kits making it available for use in poor places.

STUDY OBJECTIVE

The study aimed at evaluating the therapeutic efficacy of this newly developed machine and calculating the costs of its use.

MATERIALS AND METHODS

From January 2014 up to December 2017, we performed the HIPEC manoeuver using machine with our own design (illustrated in the next section) for ***23*** indicated patients and we recorded all the events regarding the establishing of the target temperature and maintaining it, the perfusate flow rate, technical failures, safety, the achieved results from therapeutic point of view, side effects and comparing it with those in the standard machines as published by the manufacturer. Moreover the costs which are the driving purpose for designing this machine were recorded.

All the patients were counselled and **written informed consent was obtained from all of them** regarding the manoeuvre and the expected complications

The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The study is registered in ***ClinicalTrial.gov PRS*** with ID: ***NCT04664218***

HIPEC procedure:

The procedure is done under general anaesthesia; 1 gm. of 3rd generation cephalosporin is given IV at induction of anaesthesia to be repeated 4 hours later (t ½ of the drug). The abdomen is prepared and draped in a standard fashion. A midline incision was performed which allows adequate exposure, then abdomen is firstly explored for purpose of staging according which resection limits are determined and then proceeded.

The process of HIPEC machine preparation began while the surgical resection was going on. The drugs used were determined according to tumour pathology, and the dose of the drug is calculated based on the patient's body surface, the solute we used was dextrose 5% with the dose of 1.5 L/ m2.

As the surgical procedure was going on, the stock container of the HIPEC machine is filled with the calculated amount of dextrose 5% and the digital heater is adjusted to temperature 43° and the solute is allowed to be warmed to that level but the chemotherapeutic agent was not added until then.

After completion of the surgical resection, HIPEC procedure began. New draping towels of impervious material are used to drape the abdomen and secured to the edges of the wound. The abdominal exploratory incision is shortened to allow just the hand of the HIPEC performer to pass through it by temporarily suturing the skin of the excess part of the wound. A thermo-detector probe is introduced in the abdomen with 2 catheters, one for the inflow of the heated chemotherapeutic solution and the other to return it back to chemo-perfusate stock

The abdomen had been irrigated first by the heated dextrose 5% at 41°:43° before the chemotherapy was added then after priming the abdomen with heated dextrose the chemotherapy was added. The perfusate now with a temperature of 41°:43° within the abdomen as monitored by the thermometer was maintained for 90 min, during which the perfusate is in a cycle of flowing to the patients abdomen then back to the machine, maintaining the perfusate at the above temperature for the above period within the abdomen all the time of the procedure.

The performer during that time uses his well gloved hand to homogenously distribute the perfusate within the abdomen ensuring that the chemo-perfusate contacts with all the organs and the whole peritoneal surface. After the procedure fulfils its time, the chemo-perfusate was washed out of the abdomen using normal saline 0.9% then the abdomen is closed definitively with the drains in the proper sites.

The machine of our design:

In our machine we used some tools already in use in the common life with well proved efficacy including; **A thermo-regulator (STC 3008) with double sensors, controlling output and monitors and its sensitivity is 0.1(fig. 1), two water pumps used in the household water filter whose flow rate is 2.25 L/min (fig. 2), a plastic basin can accommodate boiling water (boiling for purpose of safety), with a heater fixed in the basin, electric wires for electric circuit design, and an acrylic (or any electrically non-conducting material) box to contain all these components.**

These components are connected together using sound electrical rules and contained inside a box as shown in fig. 3 (representing diagrammatic illustration of the machine) while fig. 4&5 represent actual real life machine.

The mechanism of action:

The bag of chemotherapy stock is loaded under aseptic conditions with the selected solute (without the chemotherapy). The water basin is filled with water then the bag is immersed within the water, with its uppermost part is projecting out (as in the diagram) through which the tubes of the inflow and outflow pumps pass, also the heat sensor is introduced.

Then the process of water basin heating starts about 30 min before start of HIPEC manoeuver to obtain heated solute (to receive the chemotherapy) ready for infusion into the abdomen after completion of cyto-reduction.

The thermo-regulator has two sensors; the first detects the temperature of the chemotherapy perfusate in the bag within the water basin allowing heating of the water basin until the perfusate in the bag is between 42° and 44°. While the other sensor detects the temperature in the abdomen keeping it between 41° and 43° by activation of both inflow pump (carrying the perfusate from the heated chemotherapy stock in the bag within the basin to the patient's abdomen) and outflow pump (carrying the perfusate from the patient's abdomen back to the heated chemotherapy stock), knowing that the previous temperature values can be adjusted and changed through the thermo-regulator.

We start the session by adding 500-1000 ml (according to the abdomen capacity) of the used solution carrying the chemotherapeutic agent (at the room temperature), to the patient open abdomen (we used the open technique 'coliseum technique'). With the 2nd heat sensor placed within the abdomen and the inflow and the outflow catheters, the pumps begin to work bringing heated perfusate from the stock to the abdomen and vice versa until the target temperature (41°-43°) is reached (this happens within 2 min) then the chemotherapy is added and the process continues for 90 min.

The cycle of the above events are repeatedly and automatically going on while the operator is using his hand for symmetrical distribution of the perfusate within the abdominal cavity

The consumed (disposable) requirements per patient; **The bag containing the chemotherapy stock, the tubes connecting the stock, pumps and the patient's abdomen (four nasogastric tubes of 18 F used), two heat sensors, and the head part of the two pumps.**

Sterilization:

The above mentioned requirements are the parts which get in contact with body fluids so they are removed and disposed, bringing new ones for each patient using the plasma sterilization technique for the newly brought parts; the bag, the sensors and the head part of the pumps. The machine itself is not in need for sterilization as it doesn't get in contact with body fluids (apart from accidental splash) so it is cleaned with disinfectant solution after use.

RESULTS

All patients' data were collected, checked and analysed by using (SPSS version 20). Data were expressed as mean ± SD or number according to type of variable.

The following table ***(table 1)*** represents patient data for purpose of assessing the therapeutic efficacy and safety of the machine

Technical aspects of the machine

During the course of use of this machine, the following results were noted and recorded:

Achievement of the target temperature:

In all cases the temperature in both the chemotherapy stock and abdominal perfusate could be reached and maintained throughout the technique (90 min)

Perfusate flow rate:

As mentioned before, 2 litres of cycling flow could be achieved successfully throughout the technique

Technical failures:

Apart from loss of some of the calculated amount of the perfusate (due to occasional unavailability Thompson retractor, or any other table mounted retractor, for good abdominal exposure and maintaining enough cavity to contain the perfusate), no technical failures have been met, no obstructions in the tubes, no shooting of temperature.

Safety:

No electrical or thermal accidents ever met during its use

Costs:

According to the above mentioned components of the machine, its cost (with current price) is about three hundred and twenty US dollars (320 $)

The disposable kit for each patient costs about one hundred and ten US dollars (110 $)

It is noteworthy to mention that the above costs are taken from the acknowledgeable selling stores like amazon shopping web site and these costs may be less in other countries (in Egypt, where this machine was fashioned and used, these components were assembled and fashioned in the machine with a cost of about one hundred and sixty US dollars (160 $) and the disposable kit costs about forty US dollars (40 $)).

Table (1): Patient data

Data item		Findings / No of cases
Age		50.57 ± 9.94
Pathology		
	Colonic cancer needed resection and anastomosis	5
	Colonic cancer ended in stoma (no anastomosis)	5
	Ovarian cancer	13
Intra-operative complications		
	Surgery step	1
	HIPEC step	0
Post-operative follow-up and recorded complications		
	Return of bowel habits and start oral feeding	2.53 ± 0.47 (day)
	Hospital stay for cases with colonic anastomosis	10.28 ± 3.3 (day)
	Hospital stay for cases without colonic anastomosis	6.34 ± 1.64 (day)
	kidney dysfunction	2
	Temporary (recoverable) bone marrow dysfunction	1
	Toxic myocarditis (with consequent pulmonary complications)	2
	Intestinal fistula	No case
	Wound complications	No case
	Early post-operative mortality	3
Tumour recurrence within 3-5 years of follow-up		
	Colonic cancer cases	1
	Ovarian cancer cases	No case

Figure 1: The thermoregulator (STC 3008) controlling the temperature of both chemo. In the bag and in the abdomen

Figure 2: The pump used for the chemo cycle between the stock bag and the abdomen with its head part is disposable

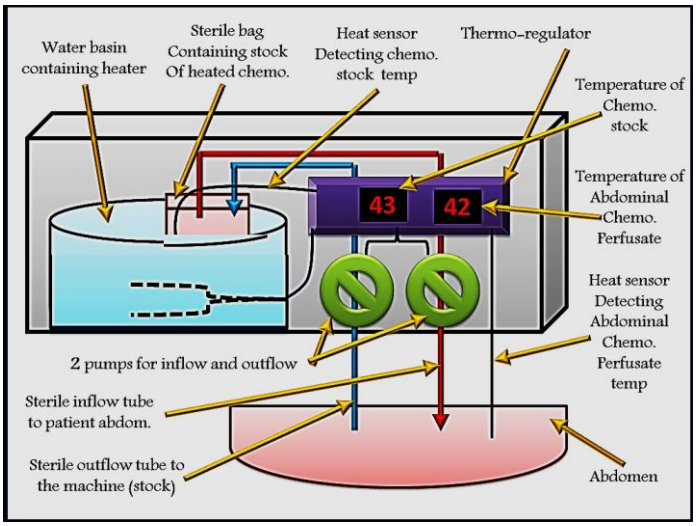

Figure 3: A diagrammatic illustration of fashioning the components to fit into the machine

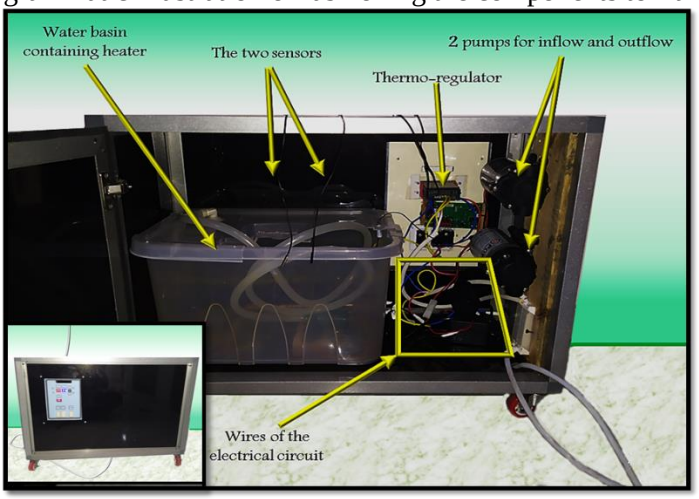

Figure 4: the real life machine of our design, illustrating its design as a posterior view (the lower right corner represents the front view)

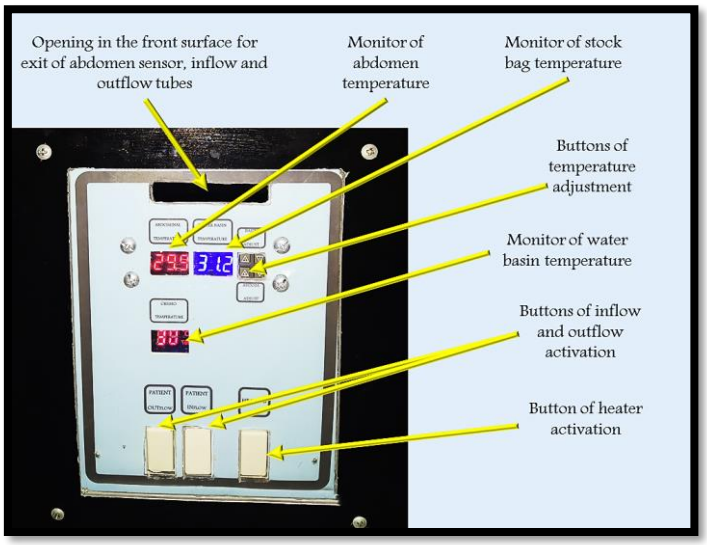

Figure 5: The front side of the machine illustrating its control panel

DISCUSSION

The concept of installation of solution containing chemotherapy for peritoneal surface malignancy is not new; Weissberger and his colleagues in 1955 reported using intra-peritoneal nitrogen mustard in treating ovarian cancer [(5)]. Although the initial results were disappointing, yet developing more understanding about suitable drug for this purpose made the results improve[(6)]. On the other hand, the lethal effects of hyperthermia on cancer cells with its mechanisms, and its synergistic effect with the heated drug were searched and emphasised [(7-10)].

Spatt and his colleagues started application of the combined intra-peritoneal chemotherapy installation with hyperthermia (HIPEC) on their dog models, and mostly done in an early post-operative [(11)]. With appearance of drawbacks, Sugarbaker was the first to apply it intra-operatively after completion of cyto-reduction [(12)]. Since then, the manoeuver came under researching and investigations with repeatedly technical improvement, and hence development of several HIPEC machines with acknowledgeable manufacturing models.

Regarding the therapeutic aspect of the machine

In our study (optimal cyto-reduction followed by HIPEC) the patients were followed up for three to five year to detect PC recurrence using enhanced pelvi-abdominal CT. We found one patient of those with colonic cancer had recurrence while those with ovarian cancer showed no recurrence. This patient had locally advanced disease with high CEA.

Almost all studies reported the same prophylactic effect of HIPEC following radical resection of colo-rectal cancer in the form of PC recurrence, provided that no synchronous PC is present at the time of primary tumour resection. In a systematic review by Honore and his colleagues in 2012 [(13)] (this review for studies published between 1940 and 2011) reported that surgery alone has rate of recurrence 11.6% compared to no recurrence when HIPEC is done.

It was noted that bowel regained its motility slower if compared to comparable operations without HIPEC, and this may be explained by the direct depressant effect of the local chemotherapy on the intestinal motility on direct contact with intestinal wall. Both Hompes et al, [(14)] and Klaver et al, [(15)] reported considerable percentage of prolonged ileus in their cases of study.

Cardio-pulmonary complications in our study patients resulted from direct toxic effect of doxorubicin on the myocardium in two patients with mild impairment that was not discovered by pre-operative investigation but could be retrograde concluded upon occasion of the complication. These findings were agreed by Klaver et al, [(15)] Vaira et al, [(16)] and Yan et al, [(17)] who had the following cardio-respiratory complication in the form of pleural effusion mainly.

The cases that underwent surgery plus HIPEC stayed for a longer period in the hospital compared to the comparable cases undergoing surgery alone (either in presence

of colonic anastomosis or its absence) and this difference is significant and mostly it is attributed to the need of some cases for ICU admission for the sake of cardio-respiratory complications and the delayed regain of bowel habits with concomitant delay in the start of oral feeding till gaining full oral intake.

These results was quite similar to the study made by López-Basave and his colleagues [18] who had nearly the same duration of hospital stay as ours, moreover Shimizu and his colleagues showed considerably longer hospital stay for patients treated with HIPEC (mean period was 15 days)

Kidney and bone marrow dysfunction were recorded in three patients being near 60 years of age. On the other hand Verwaal and his colleagues published 2 studies in 2004 [19] and 2008 [20] in which he recorded none of these complications even other complication as like cardio-respiratory; the same findings are also shared by Franko et al, [21] who reported none of these complications

In other studies like Glehen et al, [22] Mahteme et al, [23] and Varban et al, [24] small percentage of the above complications were recorded as 2.4%, 6% and 2% respectively. But higher percentage were recorded with Pilati et al, [24] and Shen et al, [25] who recorded a higher percentage of 12% and 19% respectively

In our study three patients (those passing to cardiac dysfunction and one of those with renal dysfunction) could not survive but died due to irreversible progressive deterioration of either cardiac or renal function, intractable pulmonary oedema and plural effusion.

In the study done by López-Basave and his colleagues in 2014, [18] 2 out of 39 patients (5.12%) died one due to reactionary haemorrhage 4 hours post-operative and the second massive pulmonary thromboembolism although the same researcher in earlier study 2011 recorded no early post-operative mortality at all. Other studies with their recorded mortality rate; Verwaal et al, (7.8%), [19] Sugarbaker et al, (2%), [27] Smeenk et al, (11%) [28] and Gusani et al, (1.6%) [29].

Regarding the technical and financial aspect of the machine

These standard Custom Made Machines are sold under prices that may not be afforded by poor places as its price is 40,000 $ as an average and may reach up to135,000 $, moreover the costs of consumable kit per procedure ranges between 1800-3500 $ [30].

This led to trials of designing Home Made Machines with accepted success as that made by Bhatt et al. [30], who reported their designed machine with costs of 85,000 $, (as it is a modification on the heart lung machine by adding some equipment), the costs of consumable kit per procedure ranges between 450-500 $

But as mentioned above regarding the costs in our innovation is about 320 $ and the costs of consumable kit per procedure 110 $.

On comparing our machine with those standard ones of FDA approval and that of Bhatt et al; the maximum flow rate (L/min) is 2.25 in ours, 1-2.4 in the standard ones and 7 in that of Bhatt et al

The maximum temperature that could be achieved by the machine (celsius) is 200 in ours, 46-55 in the standard ones and 100 in that of Bhatt et al. The heating mechanism used in ours is indirect heating by immersing the chemotherapy bag in warm water basin, while in the standard ones varies; heat exchanger with coil, electromagnetic induction warmer, plate heating, or medical grade anodized aluminum heat, also in that of Bhatt et al., heat exchanger with coil is used

Our machine as well as all the above mentioned have temperature adjustment and detection accuracy of 0.1°. Regarding the situation of machine use, the standard ones can be used in either closed or open ‘coliseum’ technique while ours and that of Bhatt are used with open technique only

Moreover the there is no need for technicians from the manufacturer’s side to attend and operate for the procedure as it is very simple in its use just connecting the tubes and applying the heat sensors and pressing on and it will automatically work.

RECOMMENDATION

Depending on our experience and the fact that 20% of centres in USA and some of high volume centres in Australia use other designs of Home Made Machines [30], we recommend taking the trial with further investigation to establish the efficacy

We would like to state to facts to prevent some losses:

The use of table mounted retractors is mandatory to render the abdominal cavity capable of containing the perfusate without loss

The inflow catheter should be circulated in the irrigation field of the open abdomen to prevent drug or thermal pooling (with possibility of visceral damage from intense heat).

CONCLUSION

Our design in HIPEC machine was efficient, easy to use, with no recorded complications from technical accidents or failure. Further trials can judge the results.

Author contributions:

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Conflict of interests:

The authors report no conflicts of interest.

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