Original Article

Prospective analysis of goal-directed fluid therapy vs conventional fluid therapy in perioperative outcome of composite resections of head and neck malignancy with free tissue transfer

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ABSTRACT

Background and Aim: Head and neck cancer surgeries with free tissue transfer are complex procedures, and fluid management can grossly affect the microvascular anastomosis. We hypothesise that intra-operative goal-directed fluid therapy (GDFT) is the key to administer fluid individualised to a patient's requirement. The aim of this study was to observe the role of GDFT in perioperative flap outcome and length of hospital stay. **Methods:** A randomised prospective controlled study was performed in 106 patients undergoing composite resection of head and neck cancer with free tissue transfer. Patients in Group A received GDFT based on stroke volume variation whereas Group B received conventional fluid therapy intra-operatively. The endpoints of this study were total perioperative fluid, fluid boluses, vasopressor requirement, flap outcome and length of intensive care unit and hospital stay. Statistical analysis was done using Chi-square test. **Results:** The total intra-operative fluid given to both the groups was comparable but patients in Group A received more boluses and vasopressors compared to Group B during intra-operative period. The amount of fluid given in the first 24 hours post-operatively was significantly less in Group A (1807 + 476 ml) compared to Group B (2205 + 382 ml). Incidence of hypotension with tachycardia was observed in three patients in Group B and none in Group A. Poor flap outcome was observed in one patient in Group A versus four in Group B due to thrombosis. **Conclusion:** GDFT helps in early detection of fluid deficit and may avoid complications arising due to inadequate microvascular perfusion during the peri-operative period.

Key words: Early goal-directed therapy, fluid, free tissue flaps

INTRODUCTION

Head and neck cancers are amongst the most common (30%–40%)[1] cancers in India, and surgery is the mainstay of treatment. These are long, complex procedures involving primary resection of tumour and reconstruction with free tissue transfer involving microvascular anastomosis. Optimal fluid management is crucial for microcirculation in order to sustain a healthy free flap. Fluid under-resuscitation is detrimental for anastomotic blood flow and increases the chances of flap thrombosis as well,[2,3] whereas fluid overload may lead to wound dehiscence, interstitial oedema, impaired collagen

regeneration and local inflammation, causing flap compromise.[3] The conventional method of assessing fluid requirement is based on heart rate, urine output and mean arterial pressure (MAP). During

How to cite this article: Gupta P, Chaudhari SH, Nagar V, Jain D, Bansal A, Dutt A. Prospective analysis of goal-directed fluid therapy vs conventional fluid therapy in perioperative outcome of composite resections of head and neck malignancy with free tissue transfer. Indian J Anaesth 2021;65:606-11.

surgery, flow regulatory capacities of different organs, including microcirculation, get hampered due to the effect of drugs and stress. Hence, MAP of >65 mmHg alone may not ensure a good flow in microcirculation. Additionally, there may not be any perceptible change in these indices till a patient loses one-quarter of his blood volume.[4] Stroke volume (SV) and cardiac output help in discerning the early haemodynamic derangements. In the past two decades, minimally invasive haemodynamic monitoring techniques have evolved significantly (FloTrac/Vigileo system, PiCCO and LiDCO systems), and these ventilation-based dynamic monitors can detect variation in SV with each respiratory cycle. In this context, fluid responders can be easily differentiated from non-responders by observing a favourable change in SV in response to fluid challenge and in this way circumventing potential deleterious effect of fluid overload.[5] Based on this principle, anaesthesiologists have started using goal-directed fluid therapy (GDFT) guided by stroke volume variation (SVV). SVV represents the variation of SV during ventilation cycle and values of >13% are a good predictor of fluid responsiveness.[6] In fluid non-responders, vasoactive drugs are indicated and they are safe to use as vasoconstriction does not occur in denervated flap tissue; hence, target systemic mean arterial pressure is achieved without compromise in flap blood flow.[7] We hypothesised that the detrimental effect of undiagnosed hypovolemia on free flap can be prevented using goal-directed fluid therapy by early detection and management.

METHODS

This was a randomised prospective controlled study held at our tertiary cancer care institute from February 2020 to January 2021 after institutional ethical committee approval (BMH2020/3604, dated 14th Feb 2020) and informed consent. Patients in the age Group of 18–70 years with head and neck malignancy undergoing composite resection with free tissue transfer were enrolled for this study. Exclusion criteria included patients with cardiac arrhythmia, morbid obesity, haemoglobin <10g%, serum albumin <4g%, Caprini score >8 and Charlson weight co-morbidity Index >5. The sample size was calculated at an alpha error 0.05 and study power 80% using the formula for hypothesis testing for two population mean, minimum of 42 subjects in each group, considering 5% attrition. Eligible patients were allocated Group A (goal-directed fluid therapy) or Group B (conventional fluid therapy). Group allocation was done using a computer-generated random number sequence and concealment was done by coding the sequence using a sealed envelope. The staff handling the sealed envelope was kept blind and the researcher was made aware of the allocated group in the operation theatre. Intensive care staff and surgical team monitoring the patient post-operatively were also kept blind to the group allocation to avoid bias.

Patients were kept fasting from midnight, and 200 ml apple juice was given 2 hours before surgery. In the operation theatre standard monitors (heart rate, non-invasive blood pressure, electrocardiogram, capnography and temperature) were applied to all the patients. Baseline values for heart rate (HR) and MAP were taken from the preoperative anaesthesia assessment. In Group A, FloTrac™ sensor was connected to the arterial line (radial artery) and coupled to a third-generation Vigileo™ monitor (Edwards Lifesciences, Irvine, CA, USA, software version: V03.06) to calculate cardiac index (CI) and SVV. Baseline values for SV and CI were taken after calibration of the haemodynamic monitoring system. To avoid more invasive procedures, we refrained from using a central venous catheter for systemic vascular resistance measurement. Instead, MAP was used as a guiding parameter for vasopressor administration.

A standard anaesthesia sequence was maintained in the operation theatre, and patients were ventilated at a tidal volume of 8 ml per kg body weight. Both groups received 5-ml/kg/h crystalloid Ringer lactate (RL) as maintenance fluid. In Group A, fluid bolus of 200 ml ringer lactate was given if SVV rose beyond 13%, whereas in Group B, bolus was given if MAP was <65 mmHg. Vasoactive drugs were administered only if MAP or SVV failed to improve with three fluid boluses. Mephentermine (6mg bolus) was given initially with maximum two doses and thereafter noradrenaline (when CI >2.5 l/min/m²) or dobutamine (when CI <2.5 l/min/m²) infusion was started as per haemodynamic indices.

Target haemoglobin was kept at 10 g% or above and maximal allowable blood loss was calculated using Gross' formula: $V_L = [EBV \times (H_O-H_F)]/H_O$ (V_L: Allowable blood loss, EBV: Estimated Blood Volume, H_O: initial haemoglobin, H_F: minimum allowable haemoglobin). Blood loss of >1000 ml was replaced by colloid (6% hydroxyethyl starch) initially but loss exceeding the allowable limit was always replaced by PRBC.

At the end of the surgery, we calculated the total intravenous fluid (crystalloid, colloid and packed red blood cells), blood loss and urine output. Invasive monitoring was terminated at the end of surgery in Group A. All patients were shifted to the surgical intensive care unit (ICU). Post-operative maintenance fluid Ringer's Lactate (RL) was given at the rate of 2 ml/kg/h and boluses (maximum three) of 200 ml RL were given to maintain mean arterial pressure at 65 mmHg or above. Noradrenaline infusion was started in case fluid boluses failed. Fluid intake and output charting were done till the third post-operative day.

Primary outcome of this study was post-operative flap-related complications: flap oedema, delayed circulation, venous engorgement or flap loss. Secondary outcomes were non-flap-related complications, length of ICU stay and hospital stay.

For statistical analysis, categorical variables were expressed as frequency and percentage and were analysed using the Chi-square test. Continuous variables were expressed as mean and standard deviation and were analysed using the independent sample *t*-test. $P < 0.05$ was taken as statistically significant. All statistical analysis was done using Epi info version 7.2.1.0 statistical software.

RESULT

This study was conducted on 106 patients undergoing composite resection of head and neck cancer with free tissue transfer. A total of 52 patients were enroled in Group A and 54 patients in Group B. There was no significant difference in age, gender, body mass index(BMI), American Society of Anesthesiologists (ASA) grade, risk factors and site of cancer. The average Charlson weight co-morbidity index was 2, and the Caprini score was 4–6 in all the patients. The duration of surgery was 354.1 + 56.22 min in Group A and 353.1 + 62.1 min in Group B [Table 1].

Intra-operatively, it was observed that lower MAP was recorded for Group B, with a statistically significant reading at 2 hours post incision. Also, an overall higher HR was observed with statistical significance at 4 hours [Figures 1 and 2]. Group A received a significantly higher number of fluid boluses during the first half of surgery. Thirteen patients in Group A and 3 patients in Group B received vasopressor (mephentermine, noradrenaline/dobutamine) intra-operatively, a statistically significant number.

Table 1: Baseline characteristics				
Parameter		Group A (*n*=52)	Group B (*n*=54)	P
Age	(years)	52.3±12.55	49.74±11.29	0.272
Gender	Male	45	43	0.491
	Female	7	11	
BMI	(kg/m²)	26.11±8.0	23.70±4.69	0.062
ASA grade	I	4	7	0.673
	II	46	45	
	III	2	2	
Site of Ca	Tongue	2	12	0.074
	Buccal mucosa	24	28	
	Palate	2	0	
	Lip	2	2	
	Maxilla	2	1	
	Mandible	1	0	
	Alveolus	16	9	
	GBS	3	2	
Risk factors	Alcohol	16	15	0.983
	Smoker	17	20	0.790
	Tobacco	22	17	0.344
	DM	11	7	0.389
	HTN	18	21	0.798
	CAD	1	4	0.382
	COPD	4	2	0.641
	Thyroid	5	7	0.812
	Post RT	3	6	0.523
	Revision surgery	5	4	0.954
	Post CT	3	6	0.523
Duration of Surgery	(min)	354.1±56.22	353.1±62.1	0.926

BMI-Body mass index; ASA-American Society of Anesthesiologists; DM-Diabetes mellitus; HTN-Hypertension; CAD-Coronary artery disease; COPD-Chronic obstructive pulmonary disease; RT-Radiotherapy; CT-Chemotherapy
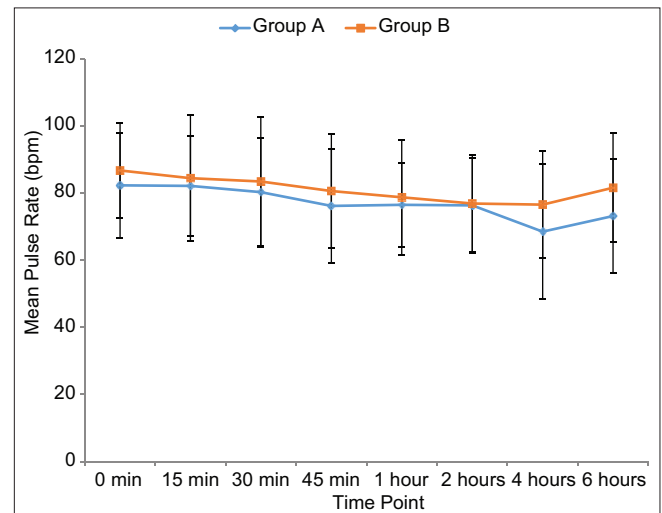

Figure 1: Intra-operative pulse monitoring

Total fluid given to Group A intra-operatively was 2781.7 + 639.5 ml and approximately the same in Group B, 2753.1 + 803.3 ml. Average blood loss was 500–600 ml in both study groups. There was a statistically significant difference in the amount of fluid given on the first post-operative

day; Group A received 1807 + 476 ml, whereas Group B received 2205 + 382 ml. From the second post-operative day onwards, there was no significant difference [Table 2].

A higher number of anastomosis-related complications, though not found to be statistically significant, were observed in Group B. In Group A, one patient recovered after re-exploration and another suffered flap failure, hence replaced with pectoralis major (PMMC) flap. Four patients in Group B had flap complications, out of which two flaps could not be salvaged and PMMC flap was done [Table 3].
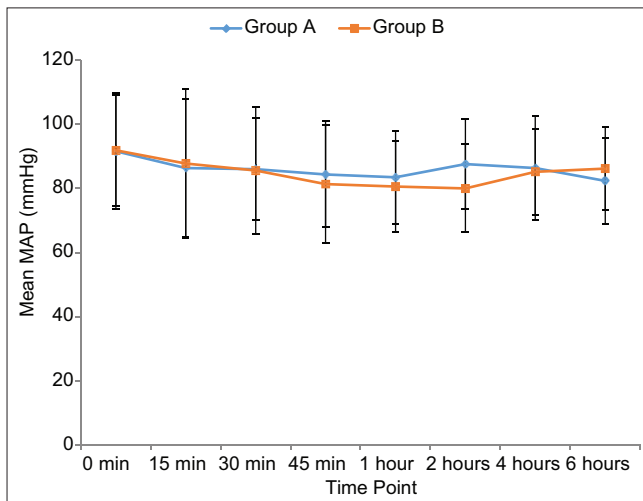

Figure 2: Intra-operative mean arterial pressure (MAP) monitoring

Non-flap-related post-operative complications in the first three post-operative days included hypotension, atrial fibrillation, myocardial infarction, pneumonitis and seizures. Incidence of hypotension and tachycardia was observed in three patients in Group B and none in Group A. One patient in Group B also developed atrial fibrillation. Two patients in each group had myocardial infarction. Post-operative pulmonary complication occurred in 2 patients in each group. One patient in Group A had a single episode of seizures. There was no significant difference among both the groups in terms of length of hospital stay.

DISCUSSION

Free tissue transfer in head and neck cancer surgeries is a complex technique and its outcome depends upon three-dimensional reconstruction with successful microvascular anastomosis. Hypotension often ensues after primary resection of the tumour as a consequence of blood loss and minimal surgical stimulus during plastic reconstruction, which can be managed by prudent resuscitation.[8,9] GDFT has emerged as a suitable technique to administer fluid in combination with vasoactive drugs tailored to the needs of the patient.[10,11] In this study, we compared the effect of GDFT versus conventional fluid therapy in the overall success of free tissue transfer and other complications. Patients with a high Caprini risk assessment score or

Table 2: Fluids and vasopressors in the perioperative period				
	Parameter	**Group A**	**Group B**	**P**
Total fluid	ml	2781.7±639.5	2753.1±803.3	0.840
Blood loss	ml	605.8±370	494.4±222.9	0.062
Crystalloid	ml	2626.9±653.5	2604.1±701.3	0.863
Colloid	ml	115.4±229.6	120.4±236.6	0.913
Blood product (PRBC)	ml	53.8±145.1	45.4±136.8	0.758
Urine output	ml	598.6±321.8	624.6±333.6	0.683
Fluid bolus in 1st half of surgery	0	4	14	<0.001*
	1	15	23	
	2	13	14	
	3	11	3	
	4	9	0	
Fluid bolus in 2nd half of surgery	0	20	21	0.974
	1	13	12	
	2	12	14	
	3	5	4	
	4	2	3	
Vasopressors	Dobutamine	3	0	0.048*
	Mephentermine	6	3	
	Mephentermine + Dobutamine	2	0	
	Noradrenaline	2	0	
	no	39	51	
Total fluid given in first perioperative day	ml	1807.3±476.5	2205.2±382.2	<0.001*

*9 patients in group A received 4 fluid boluses compared to none in group B in first half of surgery, which is statistically significant, PRBC-Packed red blood cells

Table 3: FLAP type and status			
	Group A	Group B	P
Flap			
ALT Free Flap	11	10	0.314
Double free flap	1	0	
Fibula free flap	30	25	
Radial free flap	10	18	
TFL flap	0	1	
Condition of donor Vessel			
Good	47	52	0.612
Atherosclerotic	2	1	
Calcified	3	1	
Condition of recipient's vessels			
Good	49	52	0.966
Atherosclerotic	3	2	
Unfavourable flap outcome	1 (1.9%)	5 (9.2%)	0.207
Delayed circulation	1	5	
Flap failure	1	2	

Charlson weight co-morbidity index were excluded during patient selection as they have a propensity for post-operative complications like thrombosis, wound dehiscence, haematoma and infections.[12,13]

Standard monitoring was done for patients in both groups. FloTrac™/Vigileo™ system was used for measuring SVV and CI in Group A. This device works relatively well in stable patients undergoing surgery and makes real-time adjustments to SV according to changing vascular tone and compensation in vascular compliance every minute.[14,15] Maintenance fluid was given at the rate of 5 ml/kg/h to all the patients (Clark *et al.).*[16] Intra-operative resuscitation protocol comprised administration of 200 ml of crystalloid bolus (RL) if SVV was greater than 13% in Group A or MAP decreased to less than 65 mmHg in Group B. Variation in SVV/MAP on the account of significant blood loss from 500 ml to 1000 ml was replaced by 200 ml of colloid bolus (6% hydroxyethylstarch) instead of crystalloid in both the groups till the threshold for transfusion was met.[17] But any blood loss exceeding the allowable limit was immediately replaced with blood transfusion to maintain a target haemoglobin of 10 g%, to prevent detrimental effect on flap oxygenation as stated by Hand *et al.*[18]

Hypotension was managed with maximum three fluid boluses of 200 ml each, followed by vasoactive drugs in both groups. Vasopressors direct the blood from systemic vessels to the microvascular anastomosis, favouring flap survival. A study by Fang Lin *et al.* had shown that vasopressors were used in 85% of cases of free flaps, and their use intra-operatively actually increase flap perfusion due to improved overall MAP

without significant deleterious effects.[19] In our study, 13 patients in Group A received vasopressor and only 3 patients in Group B. The higher propensity of vasopressors in Group A could be attributed to SVV-guided algorithm and early administration of vasopressors when three fluid boluses did not bring the desired improvement in SVV. Total perioperative fluid administered was found to be similar in both the groups, but the difference was that majority of the fluid boluses and vasopressors were given in the first half of the surgery in Group A unlike in the second half of surgery in Group B. This observation is in accordance with the results obtained from a pilot study by Funk *et al.*[21] GDFT helps in timely recognition of haemodynamic derangements and prompt intervention result in improved perfusion and lesser complications during the perioperative period. It has more potential to detect hypovolemia than the limited parameters we observe in our conventional approach.

The post-operative fluid requirement in the first 24 hours in Group B was higher, indicating intra-operative fluid deficit which was not observed in the study group. The incidence of hypotension and tachycardia in the post-operative period was also higher in Group B. Cecconi *et al.*[22] had reached a similar conclusion in their study, where 19 out of 20 patients in the control group had at least one episode of systolic blood pressure below 90 mmHg requiring fluid administration in the post-operative period compared to patients receiving GDFT. Peng *et al.*[23] had also observed lower HR and fewer hypotensive episodes in their patients receiving GDFT during major orthopaedic surgeries. Flap complications like thrombosis and failure were higher in Group B, four cases vs one in Group A, although it did not reach a statistical significance. Sindali *et al.*[24] concluded that the rate of complications was much less when euvolemia was maintained in their study group. In our study, the length of stay in the hospital was comparable in both the groups, which was on an average 3–4 days in surgical intensive care and 8–10 days in the post-operative ward before discharge. Trinooson C *et al.*[25] reviewed a large number of studies and concluded that the length of stay in hospital of patients receiving GDFT was significantly lower than the patients receiving conventional fluid therapy in 7 out of 12 studies.

Our study has some limitations. Iatrogenic complications are associated with invasive cardiac

output monitors. Multi-centre trials on this topic with a larger sample size are warranted in the future.

CONCLUSION

GDFT with advanced haemodynamic monitoring is a moderately liberal fluid algorithm that is helpful in maintaining perioperative haemodynamic stability and decreases the requirement of immediate post-operative fluid resuscitation. This may reduce the flap complication rate in comparison with conventional fluid therapy.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest
There are no conflicts of interest.

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