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ARTICLE

Avoiding the night terrors: the effect of circadian rhythm on post-operative urine output and blood pressure in free flap patients

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ABSTRACT
Multiple studies demonstrate the importance of goal-directed fluid regimens in avoiding complications. These regimens do not take account of circadian fluctuations in urine output (UO), MAP (mean arterial pressure) and pulse rate (PR). This is the first study that aims to demonstrate the effect of circadian rhythm on these haemodynamic parameters in post-operative patients with free flaps, as well as analysing clinicians' response to these variations. Retrospective analysis of 116 patients with free flaps. Records were assessed for UO, MAP, IV fluid infusion rate, oral fluid intake. Parameters were measured from 8 am to 8 pm (diurnal) and from 8 pm to 8 am (nocturnal) in the first 48 h post operatively. Patients with diabetes or hypertension were excluded. Mean diurnal UO rate (1.7 ml/kg/hr) was higher than nocturnal UO rate (0.7 ml/kg/hr); and mean diurnal MAP (93) was higher than nocturnal MAP (73.8). Mean diurnal IV infusion rate was 1.25 ml/kg/hr (lower) and mean nocturnal infusion rate 1.81 ml/kg/hr (higher). These differences were all statistically significant by paired student *t*-test ($p < 0.05$). This study demonstrates that circadian rhythm has a statistically significant impact on UO, MAP and PR. UO, MAP and PR are expected to dip overnight. This dip is normal and does not necessarily need to be treated by increasing IV fluids to avoid over filling of free flap patients.

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Introduction

Favourable perioperative systemic haemodynamics are important for minimising free flap anastomotic and perfusion-related complications [1]. Urine output (UO), arterial blood pressure (BP) and pulse rate (PR) are recognised surrogate markers of systemic blood flow and overall tissue perfusion [2–4]. In order to maintain adequate levels of UO and BP standard free flap post-operative care regimes in many units have incorporated intravenous fluid therapy and fluid monitoring along with flap monitoring. More recently it has been recognised that post-operative fluid overload leads to increased flap and patient oedema and may even predispose to anastomotic thrombosis in free flap patients [5–8]. This is in addition to increasing patient hospital stay and risk of other medical complications. Goal-directed fluid therapy has been developed as a means of tightly controlling fluid therapy in these patients to maintain adequate systemic circulation while avoiding complications of excessive fluids in the post-operative period [9–13].

It is well established that BP, UO and PR in normal individuals follow a distinct pattern of variation over a 24-h day period. This circadian rhythm variability naturally leads to a decrease in UO and BP at night [14–17]. Multiple hormonal and orthostatic mechanisms have been postulated for this circadian rhythm variation including increased vasopressin secretion at night, circadian variability of renin-angiotensin-aldosterone axis, changes in catecholamine and prostaglandin E2 levels, as well as change of posture and sympathetic nervous system activity [16,18,19]. Patients with Diabetes mellitus, hypertension, renal and/or endocrine pathology or other clinical situations leading to disruption in the above systems may not follow circadian rhythm as in a normal population [20].

There is paucity in the literature on whether circadian rhythm applies to haemodynamic parameters and UO in free flap patients. Furthermore, current free flap post-operative goal-directed fluid regimens do not account for any such variation. This is the first study aiming to examine whether circadian rhythm variability applies to free flap patients post-operatively, and whether any observed 'dip' in UO and BP at night leads to any adverse flap events. Also, we sought to determine if any such nocturnal decrease in BP and UO postoperatively led to excessive overall fluid administration when following a goal-directed regime. The importance of judicious postoperative haemodynamic/fluid management, which is crucial in avoiding complications in free flaps, will be discussed in this paper.

Patients and methods

Retrospective case note analysis of 116 patients with free tissue transfer. Patients had free flaps for breast reconstruction or isolated lower limb trauma. Patients with hypertension, diabetes, renal pathology or any endocrine pathology were excluded from the study. Patients with multiple injuries or BMI more than 30 were also excluded from the study. Case notes were studied for age, gender, type of free flap (i.e. trauma or breast reconstruction) and complications (flap loss and need to return to theatre for salvage). Records assessed for UO, BP, MAP, IV fluid infusion rate and oral fluid intake. Parameters were measured from 8 pm to 8 am (nocturnal) and from 8 am to 8 pm (diurnal) in the first 48 h post operatively. The first set of measurements was taken starting 8 pm on the day of the surgery. Our standard practice is to

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prescribe 125 ml/hr of Hartmann's solution in the first 12 h post operatively. This infusion rate is then titrated according to patients' urine output, blood pressure and oral fluid intake. MAP was calculated using this formula: systolic blood pressure+ 2(diastolic blood pressure)/3. We used MedCalc® statistical software to calculate paired student *t*-test, Pearson correlation coefficient and p values.

Our trust utilises 'Birmingham Systems Prescribing Information and Communications System (PICS)'. PICS is a rules-based support system that provides real-time input of data and allows for easy and accurate data retrieval (Figures 1 and 2).

Results

The total number of patients meeting the inclusion criteria was 116. Mean age was 41.8 (range 17–73). 68 of those patients had DIEP reconstruction and 48 had free tissue transfer for isolated lower limb trauma. We had four patients requiring return to theatre for salvage of free flap; two of these patients had free flap failure. The mean diurnal infusion rate was 1.25 ml/kg/hr. The mean nocturnal infusion rate was 1.81 ml/kg/hr. The difference between diurnal and nocturnal infusion rate was statistically significant using paired *t*-test ($p < 0.05$). The mean UO in the first 48 h was 1.2 ml/kg/hr; the mean diurnal urine output was 1.7 ml/kg/hr and the mean nocturnal urine output was 0.7 ml/kg/hr. The difference between diurnal and nocturnal UO was statistically significant using paired *t*-test ($p < 0.05$). The mean diurnal pulse rate was 78.6 bpm and the mean nocturnal pulse rate was 70.1 bpm. The difference between diurnal and nocturnal pulse rate was statistically significant using paired *t*-test ($p < 0.05$). The mean diurnal MAP was 93 and the mean nocturnal map was 75. The difference between diurnal and nocturnal MAP was statistically significant using paired *t*-test ($p < 0.05$). The mean diurnal oral intake was 1654 ml and the mean nocturnal oral intake was 1420 ml. The difference between diurnal and nocturnal oral intake of fluids was not statistically significant. Figures 3 and 4 demonstrate the difference between diurnal and nocturnal parameters.

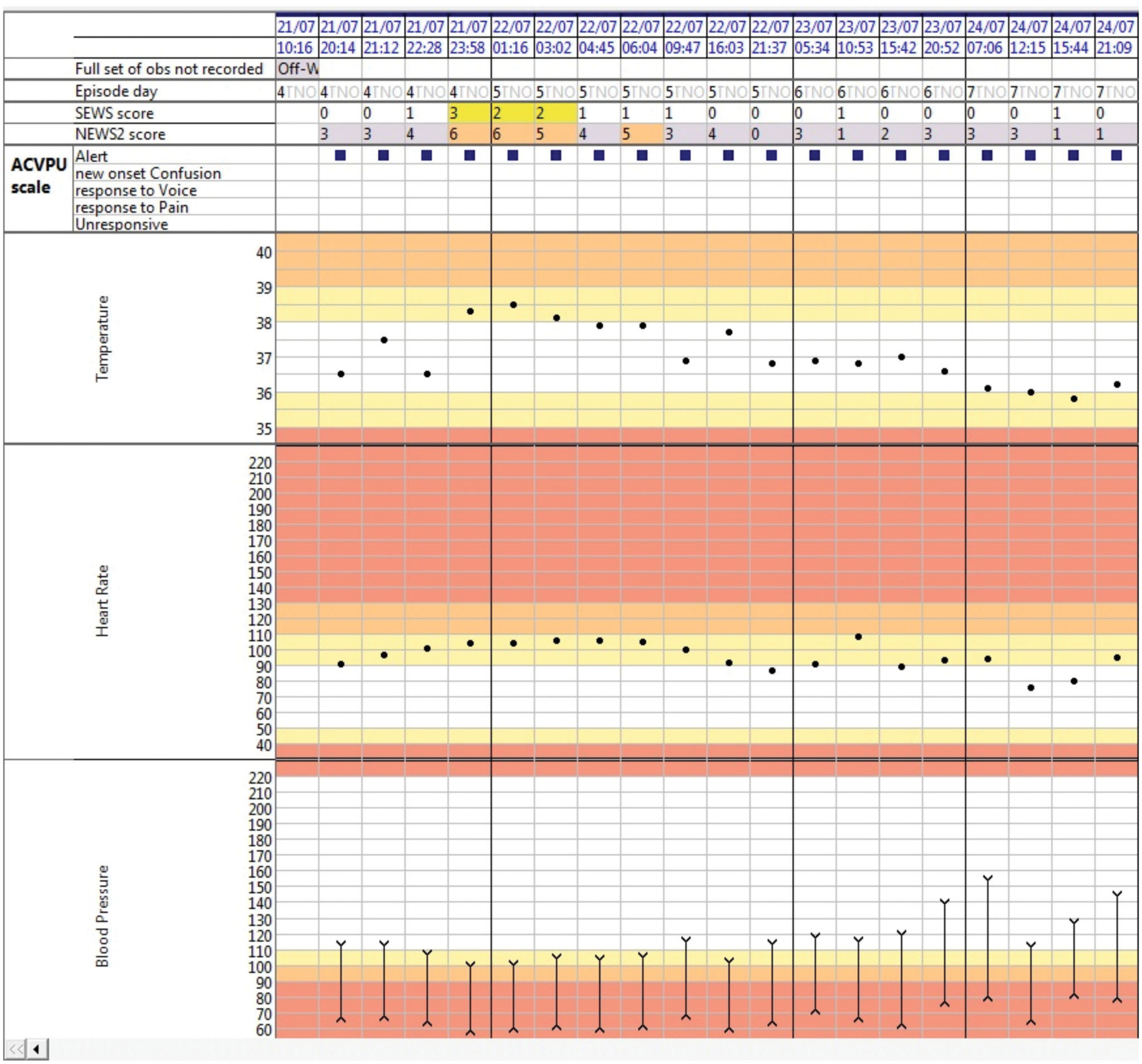

Figure 1. Screenshot of Prescribing Information and Communication System (PICS) showing patient post-operative observations after free flap procedure.

		20/07/20 13 - 14	20/07/20 20 - 21	20/07/20 23 - 00	21/07/20 07 - 08	21/07/20 08 - 09	21/07/20 19 - 20	21/07/20 20 - 21	21/07/20 21 - 22	21/07/20 22 - 23	21/07/20 23 - 00	22/07/20 00 - 01	22/07/20 01 - 02	22/07/20 02 - 03	22/07/20 03 - 04	22/07/20 04 - 05	22/07/20 05 - 06	22/07/20 06 - 07	22/07/20 07 - 08	22/07/20 08 - 09
In	Oral	100	100	100	.		0		150	50									200	200
	NG / NJ Water																			
	NG / NJ Feed																			
	NG / NJ Meds																			
	Enteral other																			
	IV Fluids: Sodium Chloride 0.45% Potassium Chloride .15% and Glucose 5%					100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	IV Fluids: vancomycin																		270	
	Subcutaneous fluids																			
	IV Blood products																			
	IV Drug Bolus																			
	IV Drug Infusion: VANCOMYCIN																			
	IV Drug Infusion: VRII							1												
	Parenteral Nutrition																			
Out	Urine			400																
	Urine Drainage other: cbd						800	250	90	105	125	45	65	60	125	175	100	100	100	125
	Vomit																			
	Aspirate (total)																			
	Drainage: Redivac						5													
	Stoma																			
	Stool																			
Balance	In (cu)	650	750	850		100	200	301	551	701	801	100	200	300	400	500	600	700	1270	1570
	Out (cu)	0	0	400		0	805	1055	1145	1250	1375	45	110	170	295	470	570	670	770	895
	Balance	650	750	450		100	-605	-754	-594	-549	-574	55	90	130	105	30	30	30	500	675
	Remarks																			

Figure 2. Screenshot from Prescribing Information and Communication System (PICS) showing post-operative urine output and fluid prescription after free flap.

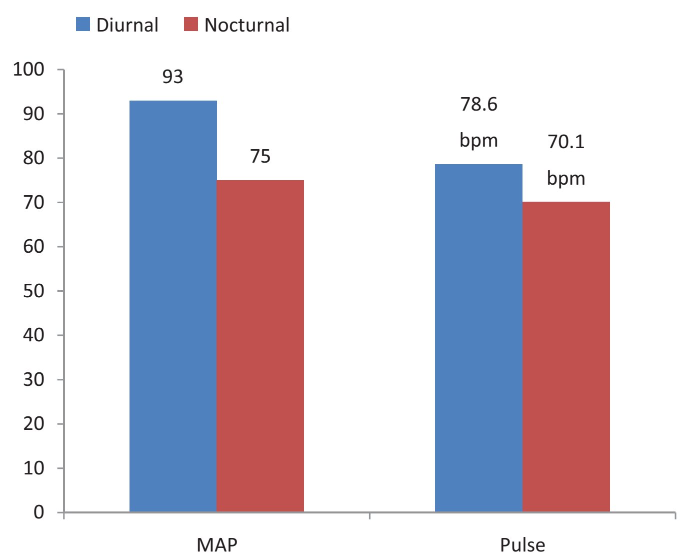

Figure 3. Mean diurnal/nocturnal overall post-operative MAP (mean arterial pressure) and PR (pulse rate) for first 48 h.

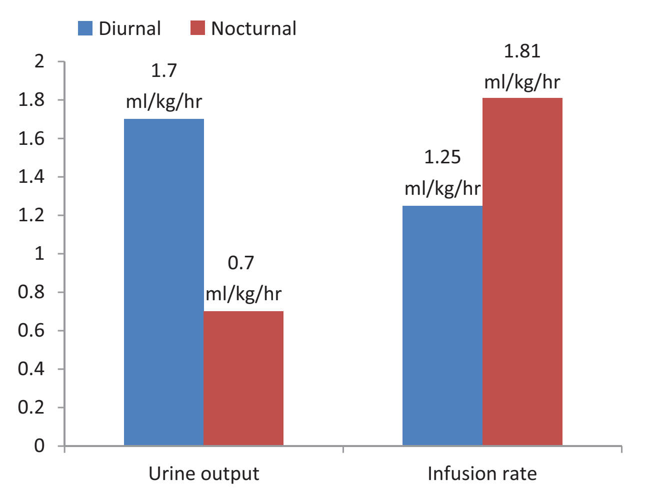

Figure 4. Mean diurnal/nocturnal overall post-operative urine output and fluid prescription for first 48 h.

Correlation analysis

In our cohort, patients were given more fluids overnight. We used Pearson correlation to identify the correlation between infusion rate and urine output. There was a weak positive correlation between the increased nocturnal IV rate and nocturnal urine output; this was not statistically significant ($r = 0.0512$, $p = 0.5$). There was no statistically significant correlation between the increased nocturnal IV fluids and MAP, pulse rate or diurnal urine output.

Discussion

Perioperative free flap care should aim to maximise overall, and subsequently flap perfusion and fluid therapy is one of the main modalities for achieving this. Maintaining adequate intravascular volume to optimise cardiac output through intravenous administration of crystalloid or colloid positively affects flap haemodynamics [1]. Previous studies have demonstrated that both intravascular depletion and fluid overload can have a deleterious effect on local and systemic perfusion in free flap patients which translates to a demonstrated increased risk of flap complications [11]. While fluid depletion leads to decreased cardiac output and increased systemic vascular resistance, overload causes excess oedema which free flap tissue is particularly prone to suffering from. This, in turn adversely affects flap blood flow and oxygenation [6]. Although some advances have been made in producing evidence-based standardised postoperative fluid therapy protocols there is still a lack of agreement on the specific regimens to be used [12,13]. Blood pressure, pulse rate and urine output are some of the standard parameters used to indicate systemic perfusion.

In healthy individuals blood pressure can reduce by an average of 10–20% to reach its lowest during night time before slowly rising in the early morning and peaking sharply after waking [14]. Urine production also reaches its lowest rate at night (up to 50% less than diurnally) [16] and is matched by a reduction in glomerular filtration rate and increased vasopressin levels [21]. These physiological variations have been well documented in the Urology and internal medicine literature [15,19]. Our free flap patient population showed nocturnal reduction in urine output (59% less than diurnal mean) and MAP (19% reduced compared to diurnal mean) in keeping with a normal population and these differences were statistically significant. The statistically significant increased nocturnal intravenous infusion rates (by a mean of 0.56 ml/kg/hr of crystalloid) in this patient group may reflect the clinical staff's response to this 'dip' by increasing intravenous infusion rates. Although our free flap protocols would only trigger increased infusion rate if UO drops below 0.5 ml/kg/hr it is possible the 'dip' in UO occurred early in the night which prompted the prescription of either fluid boluses or increased infusion rate as treatment and UO would have been expected to pick up by the early morning.

In this study, the free flap failure rate (2/116 patients or 1.7%) and return to theatre rate (4/116 patients or 3.4%) compare reasonably with other reported case series. The mean UO in the first

48 h was 1.2 ml/kg/hr indicating patients were well hydrated; however, the mean diurnal urine output was 1.7 ml/kg/hr and the mean nocturnal urine output was 0.7 ml/kg/hr. There is a possibility that our patients were displaying delayed diurnal diuresis as a result of physiological circadian variations.

As discussed, hypovolaemia in free flap patients has inherent dangers whereas fluid excess, which has received more attention recently, can lead to flap oedema, worse overall flap perfusion and risk of anastomotic thrombosis as well as potential negative medical effects [6,11,22]. This, among other factors has led to the development of goal-directed fluid therapy which also became part of various enhanced recovery protocols for free flap surgery. Consequently, there has been a measurable reduction in patient hospital stay and potentially even morbidity [9–13]. However, none of these protocols or regimes have included circadian rhythm as a consideration when deciding on fluid management. Our results highlight that the threshold for triggering increase in fluid prescription should be different for nocturnal or diurnal UO and BP.

This study was limited by the retrospective nature of data collection and the exclusion criteria of patients with high BMI, hypertension, diabetes, renal pathology or any endocrine pathology. The exclusion criteria, however, were all related to conditions which would have an impact on circadian rhythm. We calculated the physiological parameters in the first 48 h only. This is because the first 48 h are the most critical in free flap survival; furthermore our patients have the urinary catheters removed after 48 h which would make accurate calculation of urine output untenable.

Although the flap success rate was comparable with other centres, there was no objective real time measure of flap perfusion in our data. This would have been able to measure whether reduction in BP, UO overnight was related directly to any change in flap perfusion. This was not possible in the scope of our study due to its retrospective nature and as we do not routinely use non-clinical flap monitoring equipment that give a quantitative indication of flap perfusion. Our measurements took an average of UO, BP and PR overnight from 8 pm to 8am due to practical limitations of available data. However, BP especially tends to vary dynamically overnight whereby it tends to slowly drop from evening through the night and begins to rise slowly in early morning then surges to its peak on waking in the morning [14,15]. Future work may look at BP and PR in real time to correlate these changes with UO and flap perfusion. It is also possible that our data captured the early morning surge of BP in at least some patients which would have reduced the difference in nocturnal and diurnal mean BP. Other confounding factors could be that described circadian rhythm physiology in the literature most often is not related to perioperative patients who have had major surgery. Although the physiological insult of major surgery and prolonged general anaesthetic likely has some effect on normal circadian hormonal and haemodynamic controls [23], we were still able to demonstrate a convincing circadian rhythm in our patients directly post operatively. More data on the effects of anaesthetic and surgery on circadian rhythm are nevertheless needed.

Our patient set received an average of 1.81 ml/kg/hr infusion of crystalloid and 1420 ml oral fluid overnight. Some authors have suggested an ideal range of IV rate of 3.5–6.0 ml/kg/hr in the perioperative 24 h period [11]. However, this would include intraoperative fluids given which were excluded from our calculations, and these studies still advocated titration of fluid input to haemodynamic parameters and urine production [11,22,24]. Data from enhanced recovery after surgery protocol studies, which included more restrictive fluid regimes, demonstrated the safety of such practice. Moreover, survey data, at least for free flap breast reconstruction shows our practice to be in line with other UK units [25].

Conclusion

We present the first study to document fluctuation in haemodynamic parameters and urine production as related to circadian rhythm in free flap patients post operatively. Our data shows a statistically significant nocturnal reduction in UO, BP and PR when compared to daytime readings. In addition, we recorded a statistically significant increase in nocturnal intravenous fluid administration likely in response to these fluctuations but failed to demonstrate any statistically significant correlation between this increased fluid administration and nocturnal BP, UO or PR. This was all in the context of reasonable flap success and return to theatre rate. The above constitutes the first evidence that free flap patients follow well recognised circadian fluctuation patterns for UO, BP and PR and perhaps suggests that a ‘dip’ in readings overnight does not necessarily indicate a hypovolaemic state. Further to this, we have presented evidence that the increased fluid administration by clinicians did not produce the desired improvement in these parameters, perhaps as a result of a blunted responsiveness caused by normal circadian changes in hormonal and neurological factors.

Based on these findings and in the context of the larger discussion around postoperative fluid management in free flaps we recommend a more judicious approach to the prescription of intravenous fluids in response to reduction in BP and UO overnight. We also advocate a greater awareness of the effects of circadian rhythm on these parameters and caution that night-time reductions may not necessarily reflect a decrease in overall tissue and more specifically, flap perfusion.

This study carries all the limitations of a retrospective single-centre consecutive series, and further work needs to be done to precisely characterise the circadian rhythm in this group of patients, both on a basic science humoral level and also on a clinical level. Further prospective studies are also warranted to objectively examine the effects of circadian rhythm on flap perfusion and haemodynamics and ultimately flap survival as well as other complications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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