Low plasma albumin linked to fluid overload in postoperative epidural patients

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ABSTRACT

INTRODUCTION Hypotension is commonly associated with epidural use in postoperative patients and is usually treated with fluid or vasopressor therapy. The former can result in fluid overload, associated with significant morbidity. This study aimed to identify factors increasing the likelihood of fluid overload in elective patients.

PATIENTS AND METHODS A prospective audit of fluid therapy in elective, postoperative, epidural patients was carried out over a 6-week period in a teaching hospital in England. Demographic, biochemical, and fluid balance data were collected and analysed to determine which factors had the strongest correlation with fluid overload. Fluid overload was calculated as the percentage of net fluid input relative to pre-operative body weight (%FO).

RESULTS Thirty-two patients were included in this study. An overload of 10% of the patients' pre-operative body weight was considered significant. The mean fluid overload incurred by patients in this study was 8.17 l (range, 2.89–14.62 l); %FO was 11.32% (range, 3.67–26.10%). The strongest independently correlating factor to fluid overload was initial, postoperative plasma albumin. Patients with a plasma albumin less than 27 g/l developed significant overload: mean overload 9.75 l (range, 2.89–14.62 l), %FO 15.12% (range, 4.81–26.10%), whilst those with an albumin level greater than 27 g/l did not: mean overload 6.77 l (range, 3.34–11.48 l), %FO 7.96% (range, 3.67–13.93%); $P = 0.0001$.

CONCLUSIONS Patients receiving epidurals with initial, postoperative, plasma albumin levels below 27 g/l are at increased risk of significant fluid overload. Earlier instigation of vasopressor therapy in this subgroup of patients may help prevent this.

KEYWORDS

Serum albumin – Analgesia – Epidural – Postoperative period – Fluid therapy

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Modern postoperative surgical protocols focus on the accurate management of fluid and electrolyte balance in order to promote more rapid recovery. 'Fast-track' recovery programmes instituted throughout Europe have identified numerous areas to be targeted and improved in the pre- and postoperative care of patients.¹ Prevention of postoperative complications such as ileus, nausea and vomiting, and fluid overload play a pivotal role in earlier patient recuperation.^{2,3} Optimisation of analgesia and early postoperative mobilisation have been shown to be vital in achieving these goals and in preventing complications such as chest infections.⁴

One of the current recommendations to control postoperative pain is the use of epidurals.⁴ In addition to providing effective analgesia, epidurals reduce the stress response by providing sympathetic block at the level of the spinal cord with a resultant reduction in cortisol secretion.^{5–11} However, vasodilation is a significant side-effect of this sympathetic blockade and creates a relative hypovolaemic state. This

effect is compounded by loss of fluid from the intravascular space due to the post-surgical systemic inflammatory response.^{6,11,12} Hypotension is a frequently encountered side-effect and is variously managed by fluid or vasopressor therapy.^{10,11,15,14} Fluid therapy often results in overload, which in turn is associated with a myriad of well-documented complications including postoperative ileus. The relative hypovolaemia also has detrimental effects on tissue perfusion and gut wall motility.¹⁵ The goal is, therefore, to maintain an adequate mean arterial pressure to ensure organ perfusion without incurring significant fluid overload.

Vasopressor therapy has been shown to have equal, if not superior, success in correcting epidural-induced hypotension as compared to fluid therapy and avoids the side effects of fluid overload.^{11,15,14} It has been suggested that vasopressors should be used earlier in an attempt to reduce postoperative complications and enhance patient recovery.¹¹ This study attempted to identify patient factors or biochemical

markers which could identify subgroups of patients at increased risk of significant fluid overload, who may benefit from earlier institution of vasopressor therapy.

Patients and Methods

This was a prospective, non-randomised study conducted in a tertiary centre in the North-West region of England. Data were collected from consecutive postoperative patients admitted to the Surgical High Dependency Unit over a 6-week period during September to October 2007.

Demographic information was recorded for each patient including age, gender, ethnicity, operative procedure (nature and duration), and pre-existing co-morbidities. Pre-operative body weight was obtained from anaesthetic assessments which took place within a 2-week period prior to surgery. Biochemical data collected included: pre-operative estimated glomerular filtration rate (eGFR), postoperative C-reactive protein (CRP) at 24 h, 48 h and 72 h, and plasma albumin levels pre-operatively and postoperatively. The postoperative plasma albumin level was determined from blood samples taken immediately on return from theatre to the high dependency unit and this baseline value was used in subsequent analysis, eliminating confounding from dilution due to subsequent fluid administration. Epidural data included the constituents of the infusion, level of block, rate of administration, and any concomitant use of vasopressors. The mean arterial pressure (MAP), central venous pressure (CVP), and hourly urine output (UO) were collected for each patient at 4-hourly intervals over the time-period of administration of the epidural.

For the purpose of this study, patients were assumed to be euvolaemic pre-operatively. Intra-operative fluid balance was estimated from anaesthetic charts and operation notes. Operative blood loss, UO, and any other fluid losses were recorded as losses, while infusions including epidurals, intravenous drugs, and intravenous fluids administered were recorded as gains. Whilst on the high dependency unit, total fluid inputs (crystalloid, colloid, total parenteral nutrition, nasogastric feed, and blood products) and total fluid outputs (UO, stoma losses, drain losses, vomiting, and nasogastric tube losses) were recorded at 12 h postoperatively and at the end of every subsequent day until the epidural was removed.

Previous studies have defined excessive fluid overload either as a percentage of body weight or as an absolute value. As recording absolute cumulative fluid balance does not cater for variations in baseline bodyweight, percentage fluid overload was used in this study. Lowell *et al.*¹⁶ defined significant fluid overload as an increase in body weight of 10%. More recent papers suggest that a fluid overload of 5–6 l is significant but have not expressed this figure as a percentage of pre-operative body weight.^{17–20} In this study, an overload of 10% was considered significant.

Net fluid balance was calculated as the difference between total fluid input and total fluid output. Net fluid balance was then expressed as a percentage of the patient's pre-operative body weight:

$$\text{Percentage fluid overload (\%FO)} = \frac{\text{Net fluid balance}}{\text{Pre-operative body weight}} \times 100 \quad \text{Eq. 1}$$

Statistical analysis

Statistical analysis was performed using SPSS v.16.0 (Windows). All charts and graphs were produced using either SPSS or Microsoft Office Excel 2007.

Pearson correlation was used to determine which factors significantly affected %FO and to determine the relationships between other variables. A 2-tailed *P*-value of 0.05 or less was considered significant and *P*-values less than 0.01 were considered highly significant. To determine significance after controlling for confounding or contributing factors, partial correlation was used. Categorical data, such as gender, were analysed using contingency tables and significance was determined by applying Pearson's chi-squared test or the Kendall Tau test.

Linear regression, binary logistic regression (overload/no overload) and non-linear regression were then used to determine further the nature of the relationship between significant factors. Significant criteria identified were compared to determine which factors were most predictive of %FO. Equations produced using regression analysis were used to determine when significant fluid overload occurred. Where appropriate, the Student's *t*-test and Fisher's exact test were used to determine if observed differences in %FO between groups were significant.

Results

Thirty-six consecutive patients were enrolled in the study. Of these, four patients were treated with vasopressors and were excluded.

The mean fluid overload of all patients was 8.17 l (range, 2.89–14.62 l), corresponding to a %FO of 11.32% (range, 3.67–26.10%). Mean duration of epidural insertion was 2.6 days (range, 1–6 days) and the median day of maximal overload was day 2 (Fig. 1).

Pearson's chi-squared test demonstrated no significant difference between overload in males (mean, 11.35%) and females (mean, 11.28%; *P* = 0.529). Patients undergoing different types of surgery and those in different age groups were divided into those who incurred fluid overload and those who did not. These data were entered into contingency tables and analysed using the Kendall Tau test. No significant difference was found between different types of operation or age groups.

Figure 1 Histogram depicting the number of days post-epidural insertion maximal fluid overload occurred. Maximal overload occurred most commonly on day 2.

Linear regression and partial correlation were used to determine which variables had the strongest correlation with percentage fluid overload. The variables analysed included the demographic, biochemical, physiological, and epidural-related parameters as described above.

The mean pre-operative albumin level was 42 g/l (range, 29–49 g/l) and the mean postoperative plasma albumin was 26 g/l (range, 10–38 g/l). Immediate postoperative plasma albumin was normally distributed.

Pre-operative body weight, duration of epidural use, immediate postoperative albumin, and mean MAP over the first 12 postoperative hours correlated with %FO; however, controlling for postoperative plasma albumin, other variables ceased to correlate significantly. Immediate postoperative albumin correlated independently of other variables and multinomial logistic regression showed that it had the strongest correlation with %FO ($P \leq 0.0001$). Regression analysis was used to determine the nature of the relationship between %FO and postoperative plasma albumin.

Using the equations and graphs produced from regression analysis, it was determined that significant percentage fluid overload occurred when the immediate postoperative plasma albumin was at a level of 27 g/l or lower. This, our key finding, is summarised in Figure 2.

The mean maximum fluid overload of patients with an immediate postoperative plasma albumin of greater than 27 g/l was 6.77 l (range, 3.54–11.48 l) and the mean %FO was 7.96% (range, 3.67–13.93%), whereas for patients with albumin levels lower than 27 g/l the mean value of maximum overload was 9.75 l (range, 2.89–14.62 l) and the mean %FO was 15.12% (range, 4.81–26.10%). A Student's *t*-test performed on these data shows that this is a highly significant difference ($P = 0.0001$). The odds ratio for significant overload in patients with albumin levels of less than 27 g/l

Figure 2 Relationship between percentage fluid overload and immediate postoperative plasma albumin. Trend line demonstrates inverse logarithmic relationship. Dashed lines demonstrate that 10% fluid overload occurs when immediate postoperative plasma albumin is lower than 27 g/l.

as compared to those with higher albumin levels was 12.8 ($P = 0.004$ using Fisher's exact test). The mean maximal overload for patients with postoperative albumin levels lower than 20 g/l was 10.35 l (range, 2.89–14.62 l) and the mean %FO was 16.24% (range, 4.81–26.10%).

Discussion

Patients with excessive fluid overload postoperatively have longer lengths of hospital stay and an increased incidence of complications.^{2,3,18,21} The postoperative use of fixed fluid regimens does not take into account a variety of patient factors and is less useful than goal-directed fluid therapy which aims to attain euvolaemia.^{17,22–24}

The average fluid overload incurred during this study was 8.17 l (%FO = 11.32%). Immediate postoperative plasma albumin correlated most significantly to, and independently of, %FO. Recent studies investigating the effects of hypoalbuminaemia on rates of complications found that absolute levels of albumin are more important than percentage changes.^{12,25} One cause for a postoperative decrease in albumin levels is dilution by intra-operative fluid administration.¹² The link between albumin and %FO is not surprising as low plasma albumin levels result in decreased plasma oncotic pressure.²⁶ Furthermore, the inflammatory and stress responses after surgery result in a decrease in albumin synthesis and an increase in capillary permeability.^{6,12,27,28} Consequent extravasation of fluid into the extravascular compartment causes a reduction in MAP and predisposes the patient to incurring significant overload. Albumin levels are likely to remain low due to the on-going systemic inflammatory response.

This paper aims to identify an immediate postoperative albumin level at which significant overload is likely to occur if only fluids are used to correct epidural-related hypovolaemia. Using the regression models produced, an albumin level of 27 g/l was found to correlate with significant fluid overload (> 10%). This suggests patients with immediate postoperative albumin levels lower than 27 g/l are at risk of developing fluid overload if treated with fluid therapy alone.

Maximal overload occurred most frequently on day 2 (Fig. 1) but the mean duration of epidural insertion was 2.6 days. The systemic inflammatory response normally begins to abate after 2 days^{21,29} with a resultant return of fluid from interstitial to intravascular spaces. Continued epidural use, however, sustains vasodilation and blunts this effect. Duration of epidural does not, however, serve as a good predictive factor for overload as maximal overload tends to occur early. The MAP is often used as a marker of tissue and gut perfusion and, frequently, as a trigger for initiating fluid therapy. A persistently low postoperative MAP over the first 12 postoperative hours was significantly correlated with overload, likely due to repeated fluid challenges. Fluid administration tends to decline after the first day as the relative hypovolaemia is corrected but by this time the patient may have already become overloaded. Vasopressor therapy would, therefore, ideally need to be instituted by the first postoperative day in those with a persistently low MAP in order to avoid fluid overload.

These results suggest that immediate postoperative albumin is one of the most useful predictors of whether an elective epidural patient is likely to incur significant fluid overload and that overload becomes established early. We hypothesise early, targeted vasopressor therapy may offset overload in this subgroup of patients. Unfortunately, vasopressor use is not without its side-effects and risks and its use must be tailored to individual need. In particular, patients with an immediate postoperative albumin of less than 20 g/l incur very high risk of significant fluid overload and should be strongly considered for vasopressor therapy before the second postoperative day unless there are strong contra-indications to their use.

This study does have a number of limitations. The number of patients included was 32 and a larger study could better qualify these observations. The patients included were from a variety of specialties, which we acknowledge may have different fluid-balance issues. Another limitation was the method of estimation of peri-operative fluid balance. Records kept were accurate, but insensible fluid losses have not been accounted for. This could be avoided by determining fluid balance using serial body weight measurements, but the logistics of organising this in our setup were significant. Although this study aimed to determine which patients would be more likely to benefit from vasopressor

therapy, the number of patients who actually received vasopressors (four) was too small to draw any significant conclusions. Future studies or randomised control trials would be valuable in assessing the efficacy of our hypothesis on a larger patient population.

Conclusions

This study aimed to identify factors which would be predictive of overload in epidural patients in order to allow earlier institution of vasopressors. Immediate postoperative plasma albumin was found to be the best, independent predictor of likelihood of significant fluid overload and maximal overload was found to occur most commonly on postoperative day 2. Other risk factors identified included low body weight, a low postoperative MAP and a longer duration of epidural use. In elective patients with postoperative albumin levels of 27 g/l or below, fluid therapy alone is likely to result in a significant degree fluid overload and overload is particularly marked in patients with plasma albumin levels of less than 20 g/l.

Based on these findings we hypothesise that early instigation of vasopressor therapy in patients with albumin levels lower than 27 g/l may help avoid overload in this subgroup of patients. Future trials will be needed to determine whether this mode of intervention has a significant impact on reducing patient fluid overload.

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