Is Low Albumin Associated With Post-operative Pharyngo-cutaneous Fistula?

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Abstract

Objectives: Low albumin is associated with poor outcomes in critically ill patients, whilst malnutrition leads to impaired wound healing. As low albumin has been used as a marker of malnutrition and stress response, we hypothesised that low albumin may be a risk factor for pharyngo-cutaneous fistula after surgery involving a pharyngotomy. The objective therefore was to compare mean lowest albumin levels after surgery involving a pharyngotomy between patients who did or did not develop a post-operative fistula.

Methods: Prospective collection of lowest in-patient albumin level after any surgery, by single surgeon (JS), involving a pharyngotomy. Statistical analysis by t-test using SPSS.

Setting was an NHS secondary care ENT/Head & Neck Unit. Participants were all patients having procedures involving a pharyngotomy under care of a single consultant (JS) between Sept 94 and Feb 07. The main outcome measures was fistula rate.

Results: 75 patients had 81 procedures: 31 total laryngectomy, 18 total laryngectomy/partial pharyngectomy, 15 total pharyngo-laryngectomy, 9 partial pharyngectomy or partial laryngectomy or both, and 4 pharyngeal pouch excision, and 4 other procedures. 7 patients developed a pharyngo-cutaneous fistula. Lowest post-op albumin levels ranged from 7-42 g/L, mean 22.96 g/L. Mean albumin in group developing a fistula was 20.43 g/L, and in group with no fistula 23.20 g/L; the difference was not statistically significant (p=0.24) (93% power to detect 3g/L difference, $\alpha=0.05$).

Conclusions: No significant difference was observed in albumin levels in patients with or without post-operative fistula, suggesting that low albumin may be neither associated with nor a contributing cause of pharyngo-cutaneous fistula.

Introduction

Pharyngo-cutaneous fistula (PCF) is a serious complication of (pharyngo)laryngectomy, and an important outcome that should be monitored by individual surgeons for the purpose of clinical governance. An incidence of PCF between 9 and 23% has been reported[1,2] Various factors have been implicated (Table 1), but occurrence often still cannot be predicted.

Malnutrition is recognised as an important factor contributing to poor wound healing and a high rate of post-operative complications [3,4,5,6,7] with weight loss itself predicting poor survival in Head & Neck cancer [8,9]. In humans, albumin is the most abundant plasma protein, and low albumin levels have been associated with poor ITU outcomes [10] and wound complications [11]. Albumin levels may be low pre-operatively due to malnutrition, but levels also fall post-operatively as part of the acute phase reaction due to reduced production, increased destruction, increased trans-capillary loses and redistribution.

As low albumin has been used as a marker of malnutrition and stress response, we hypothesised that low albumin may be a risk factor for pharyngo-cutaneous fistula after surgery involving a pharyngotomy. The aim of the study, therefore, was to measure mean lowest albumin levels after surgery involving a pharyngotomy, comparing albumin levels in those patients that developed a post-operative fistula with those that did not. If an association was found, low albumin may be used as a predictive factor, and could be investigated as a potential therapeutic target.

Methods

Patients

All patients having any form of surgery involving a pharyngotomy under the care of a single consultant (JS), between 27th September 1994 and 24th February 2007, were included in the study.

Data collection

Data was collected prospectively by the senior author.

Measurements & outcomes

Albumin levels were checked post-operatively as part of routine patient care, and lowest level during in patient stay recorded. Post-operative pharyngo-cutaneous fistula was diagnosed according to standard clinical practice with a combination of clinical assessment and/or contrast swallow.

Statistical analysis

Power calculation was performed on website dssresearch.com, with SPSS used for statistical analysis.
Ethical considerations
Routine patient data was collected on a purely observational basis. Patients' care was in no way influenced by this study.

Results
A total of 75 patients had 81 procedures involving a pharyngotomy between September 1994 and February 2007; their characteristics are shown in Table 2. Of these, 7 patients developed a post-operative pharyngo-cutaneous fistula.

Mean lowest albumin level in patients developing a fistula was 20.43 g/L, whereas in the group without a fistula it was 23.20 g/L. The difference was not statistically significant (t test, p=0.236), with the study having 93% power to detect a 3g/L difference with α 0.05.

Pre-operative radiotherapy did not affect fistula rate, which was 7.9% (5/63) in patients without radiotherapy, and 11.1% (2/18) in patients with radiotherapy (Fisher’s exact test p=0.648). Additionally, pre-operative radiotherapy also did not affect lowest albumin level, which was 22.81 g/L without radiotherapy and 23.50 g/L with radiotherapy (t-test p=0.664).

The type of surgery performed did not affect leak rate (Fisher’s exact test p=0.724). Performing a surgical procedure additional to main surgery involving pharyngotomy (e.g. neck dissection) did not affect fistula rate, which was 4.2% (1/24) without additional surgery, and 10.5% (6/57) with additional procedures (Fisher’s exact test p=0.668). However, additional surgery significantly reduced lowest albumin level from 26.29 g/L in patients without additional surgery to 21.56 g/L in those with extra procedures (t-test, p=0.001).

Age did not affect either fistula rate (8.1% (3/37) in patients and de Zinis et al[13] (246 patients), who examined pre- and post-operative albumin levels and found no effect on rate of fistula formation. However, another study of over 2000 patients found that wound complication was associated with pre-operative hypo-albuminaemia [14], and a further two studies (100 and 155 patients, respectively) also suggest that low albumin may play a role [15,16].

It is possible to explain these disparate findings if one examines how and when albumin levels were measured. Our study measured only post-operative levels and comparison can therefore only be made with other studies measuring the same (the difference between pre- and post-operative albumin levels is discussed later). Whereas this study measures lowest in-patient post-op alb level recorded and compares means, Morton measured albumin level on day 3 post-operative comparing means, and de Zinis measured albumin level on day 5 post-operative and compared fistula rates in patients with albumin levels. Thus, comparing our findings with other studies that measure post-op albumin levels, the finding of no PCF association is confirmed. However, our study is the first to look at mean lowest albumin level during in-patient stay, rather than level on a set post-op day.

Strengths and limitations
The study took place in a single unit under the care of a single consultant, thereby significantly reducing variability related to pre-, intra- and post-operative management. Patients were defined and data collected prospectively. A variety of different surgical interventions were included in this study, for both benign and malignant conditions which, while increasing general applicability, may act as a confounding factor. However our data have not shown any significant difference in leak rates between groups undergoing different or additional procedures. Similarly, although radiotherapy itself was not associated with greater fistula rate, neither radiotherapy nor any of the multiple other factors associated with fistula formation were corrected for in the study, which focused particularly on albumin with the aim of generalisability. This study measured only post-operative albumin levels and the frequency of measurement was based on clinical assessment rather than on a protocol. This is likely to have introduced variation in timing and frequency of collection. Additionally, the sickest patients are likely to have had more frequent albumin measurements. It may also be interesting to examine the effect of pre-operative albumin levels. Pre-operative levels may reflect longer-term nutrition status and general health, whereas post-operative levels will be influenced by the surgery itself, fluid balance, and nutritional replacement regimens.

Discussion
Synopsis of key findings
This study has not shown an association between low post-operative albumin and pharyngo-cutaneous fistula post major pharyngeal surgery. Age, pre-operative radiotherapy, type of surgery, or performing additional surgical procedures also did not influence fistula rate.

Comparison with other studies
These findings agree with Morton et al [12] (102 patients) and de Zinis et al[13] (246 patients), who examined pre- and post-operative albumin levels and found no effect on rate of fistula formation. However, another study of over 2000 patients found that wound complication was associated with pre-operative hypo-albuminaemia [14], and a further two studies (100 and 155 patients, respectively) also suggest that low albumin may play a role [15,16].
Albumin as a marker of nutrition and stress response

Although serum albumin concentration may be used as a surrogate marker of nutrition, its relatively long half life does not provide an accurate reflection of nutritional status [17,18]. Even during chronic malnutrition, serum albumin concentration is maintained because of a compensatory decrease in the degradation of albumin and transfer of extra-vascular albumin to the intravascular compartment. Better markers of nutrition have been identified, such as prealbumin, retinol-binding protein and transferrin, although even these do not always correlate well with nutritional status. Various formulae based on combining different plasma protein measurements have been proposed, as has the use of anthropometric measurements. Hence, in order to examine impact of nutrition on PCF, albumin should not be chosen as it is a poor index of malnutrition.

Although inadequate nutrition may contribute to low serum albumin concentrations in patients in hospital, the metabolic response to stress (for example, surgery and disease) is a far more important factor. In such "inflammatory stress" states, synthesis of albumin decreases and degradation and transcapillary losses of albumin increase. In patients with acute and chronic illness serum albumin concentration is inversely related to risk of death, leading to albumin levels being incorporated into the Acute Physiology and Chronic Health Evaluation score. A systematic review of cohort studies meeting specified criteria estimated that for each 2.5g/l decrement in serum albumin concentration the risk of death increases by between 24% and 56% [19]. Partly as a result of the association between serum albumin and mortality, the use of human albumin solution has been trialed in critically ill patients. However, a meta-analysis suggested that far from being beneficial, albumin use may have resulted in additional deaths [20], calling for more research and sparking a controversy about albumin use.

Given that low albumin post-op (marker of "stress") has been associated with poorer outcomes, why has this study not found evidence of an association between low albumin and PCF? This lack of an association suggests either that low post-op albumin is not a good marker of systemic illness after major head & neck surgery, or that systemic illness is not a major factor in PCF aetiology.

Reducing PCF rate

Despite numerous factors being implicated in PCF, it is still difficult to predict which patients will suffer this complication. However, some proposals have been made with the aim of reducing PCF rate, including optimization of co-morbidities such as diabetes, anaemia and malnutrition [21], and the use of prophylactic antibiotics [22]. Surgical factors are also important, with meticulous attention to technique, and perhaps the use of free vascularised tissue transfer to re-enforce neopharynx suture line in patients at high risk of PCF due to prior chemo-radiotherapy [23]. It also beholds individual surgeons to monitor their own PCF rate for purposes of audit and clinical governance.

Clinical applicability

Low albumin cannot be used as a marker of fistula risk, although attention to nutrition remains an important factor in Head & Neck cancer management.

Conclusion(s)

This study supports the opinion that a low albumin level after surgery involving a pharyngotomy is not a predictor for PCF.

Reference(s)

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