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Serum lactate as a marker of mortality in patients with hip fracture: A prospective study

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ABSTRACT

Outcomes from patients suffering hip fracture remain poor, with 9% mortality at 30 days and 35% at 1 year. Despite robust guidelines these mortality rates have undergone little change. Admission serum lactate in patients with sepsis or suffering general trauma has been shown to be an indicator of adverse clinical outcomes. We investigated whether venous lactate can predict mortality for hip fracture patients.

Over a 12-month period the admission venous lactate of all patients presenting to our institution with hip fractures was prospectively collated. Demographic and patient survivorship data were also prospectively recorded. Multivariate binary logistic regression and Cox proportional hazards ratio analysis was used to evaluate the relationship between admission venous lactate and 30-day mortality and early survivorship, whilst adjusting for age and gender.

770 patients were included in the study. The mean age was 80 years. The overall 30-day mortality for this cohort was 9.5%. Admission venous lactate was associated with early death. A 1 mmol/L increase in venous lactate resulted in a 1.9 (95% CI 1.5–2.3 $p < 0.0001$) fold increase in the odds of 30-day mortality and a 1.4 (95% CI: 1.2–1.6 $p < 0.0001$) factor increase in the risk of death at any time after hip fracture. Admission venous lactate remained a predictor of mortality despite adjustment for patients American Society of Anesthesiologists (ASA) grade. Those with an admission serum lactate of 3 mmol/L or greater were particularly at risk. This cohort had a 30-day mortality odds that was 5-fold higher than those whose level was less than 3 mmol/L ($p < 0.0001$) and at any-time risk of death that was 1.9 times higher ($p < 0.0001$). Those with a level of less than 3 mmol/L had a 30-day mortality of 6.8%. For those with an admission venous lactate of 3 mmol/L or greater this was four times higher at 28%. The difference was statistically significant ($p < 0.0001$).

Elevated admission venous lactate following hip fracture is a predictor of early death. Venous lactate may be useful as a prognostic indicator or risk stratifier in patients with proximal femoral fractures.

Introduction

Hip fractures are a very common injury and a global problem. There were approximately 1.6 million such fractures worldwide in 2000 [1] and this is expected to increase to 21 million in 2050 [2]. The 2012 National Hip Fracture Database indicated there are 70 000 cases annually in the UK representing one case per 1000 population [3]. In the USA a higher incidence has been shown with seven cases per 1000 for women and four cases per 1000 for men [4]. The lifetime risk for the UK and USA population has been estimated at 11% for men and 22% for women [5].

Hip fractures are the most lethal manifestation of the global osteoporosis pandemic. They are associated with a very high morbidity and mortality. In-hospital, 6 month and 1 year mortality rates are reported at around 11%, 16% and 35% respectively [6,7]. Such persistently high mortality rates suggest that the pathophysiological mechanism responsible for adverse outcomes following hip fracture are not being fully addressed .In hip fracture the clinical outcome appears out of proportion with injury sustained

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and non-injury factors determine outcome. The hip fracture clearly has a profound affect on patient physiology. A similar effect is seen in multiply trauma where some patients develop a widespread systemic inflammatory response syndrome (SIRS) [8]. In these individuals the mortality can be much higher than that predicted from the sum of the individual injuries. In major trauma serum lactate has been identified as predictor of outcome [9]. Hyperlactaemia is the result of anaerobic respiration and a marker of uncompensated hypoperfusion. Serum lactate can be used as a common endpoint to evaluate the degree of physiological insult suffered by patients who may have endured a heterogeneous cluster of injuries and who have differing physiological reserve and pre-morbid state. Lactate thus acts as a biochemical index of the severity of injury and has been instrumental in understanding the pathophysiology of the multiply-injured patient [11].

We wondered if in elderly patients with limited cardiovascular reserve, a hip fracture might be physiologically equivalent to more severe injuries in a young patient and, that lactate might act as a patient-specific index of the severity of physiological insult suffered following hip fracture that would automatically factor in the patient's pre-morbid condition. In a retrospective study we showed that lactate was in fact a prognostic indicator in patients with hip fracture [10]. However, as the study was retrospective there was the possibility of selection bias in the cohort of patients for whom lactate was available. We therefore decided to undertake a prospective study and we sought to determine if serum lactate was a prognostic indicator in patients with hip fracture.

Methods

On arrival at the emergency department to our university hospitals, all patients with hip fractures undergo near-patient testing (Roche cobas b 221) [16] for standard blood parameters, including serum venous lactate. We prospectively collected demographic and admission venous lactate data on patients who presented with a hip fracture between June 2011 and May 2012. Fracture pattern and mode of fixation were also noted. If patients sustained a hip fracture as part of polytrauma (injury severity score (ISS) $>$ 15) [17] they were excluded.

We explored the relationship between admission venous lactate level and mortality adjusting for potential confounders. Previous studies have identified a venous lactate of 3 mmol/L as a reliable discriminator between those suffering adverse outcomes and those having more favourable outcomes [11–13,25]. This has been corroborated in a number of clinical contexts [13–15,23].

We analysed the data to determine whether the 3 mmol/L lactate level could be applied to patients with hip fractures when correcting for age and gender. American Society of Anaesthesiologist (ASA) grade was determined from data entered into the National Hip Fracture Database. No funding was received for the study.

Statistical analysis

Comparison between continuous data was performed using two sample *t*-tests. Shapiro-Wilk pre-analysis confirmed continuous data were normally distributed. Categorical data were compared with χ^2 tests. Multivariate binary logistic regression was used to determine adjusted odds ratios for 30-day mortality. We complied with the guidelines espoused by the American College of Physicians for performing and reporting logistic regression analysis [18]. The assumptions of logistic regression were verified prior to the inclusion of co-variates (there was no correlation between the variables). Cox proportional hazards ratio was used to determine the effect of serum lactate levels on survivorship. Kaplan–Meier curves were constructed and compared for using the log-rank test.

Results

863 patients presented to our institution in the relevant time period with hip fractures. All patients were registered in the UK National Hip Fracture Database. For 93 patients no lactate level was recorded, which, was due to two reasons. First, there was no result in 53 cases when the near-patient testing machine was undergoing calibration, servicing or giving an error reading. Secondly, 40 patients suffered their hip fracture whilst already on a hospital ward and hence did not undergo near-patient testing, which is only performed in the accident and emergency department. Therefore a total of 770 patients with measured lactate levels comprised our cohort.

The mean age was 80 years (range 31–105 years). 90% of the patients were 65 years of age or over. The male:female ratio was 1:2.8. Ninety six percent underwent surgery, with a median time to surgical intervention of 24.1 h (range: 1–246 h). The overall 30-day mortality was 9.5%.

Lactate as a continuous variable

Using *multivariate binary logistic regression* adjusting for age and gender, increased lactate levels were found to be associated with increasing risk of 30-day mortality (see Table 1). For any given age and gender, there was a 1.9 (95% CI 1.5–2.3, $p < 0.0001$) rise in the odds of *30-day mortality* for each 1 mmol/L rise in venous lactate. Increasing age and male gender was also associated with an increased risk of in 30-day mortality. Table 1 shows that for every year increase in age the odds of death at 30 days rises by a factor of 1.1 ($p < 0.0001$). Similarly female sex is associated with 0.25 factor reduction in the odds of 30-day mortality ($p < 0.0001$).

ASA Grade is clearly not a biochemical marker of disease but rather a synthetic marker of pre-morbid condition. To ensure that the lactate was not a surrogate marker for ASA Grade, in a separate analysis adjustment was made for ASA Grade in addition to age, gender and lactate levels. Following this adjustment, using logistic regression serum lactate remained a potent predictor of 30-day mortality ($p = 0.0001$ odds ratio 1.6 95% CI: 1.3–2.1). Hence for any two patients of the same age, gender *and ASA Grade*, the patient with the higher venous lactate level on admission has the higher risk of 30-day mortality. Indeed for every 1 mmol/L difference there is a 1.6 increase in the odds of 30-day mortality.

We performed *Cox proportional hazard analysis* correcting for *age and gender* to determine whether increased admission venous lactate engendered a higher mortality for the *entirety of the study period*. The results are shown in Table 2. *At any given time* the risk of mortality following hip fracture rises by a factor of 1.4 for every 1 mmol/L rise in admission venous lactate (95% CI: 1.2–1.6 $p < 0.0001$).

Lactate <3 mmol/L vs. *lactate ≥3 mmol/L*

The 649 patients with serum lactate of less than 3 mmol/L had a 30-day mortality of 6.8% which was significantly lower on univariate analysis than the mortality (28%) in the 121 patients

Table 1
This shows the result of multivariate logistic regression on the effect of admission venous lactate in patients with hip fracture; adjusting for age and gender. F: female, M: male.

Factor	*p*	Odds ratio	Odds ratio lower (95%)	Odds ratio upper (95%)
Lactate	**<0.0001**	1.86	1.50	2.30
Age at event	**<0.0001**	1.1	1.07	1.15
Gender F vs. M	**<0.0001**	0.25	0.15	0.43