The Utility of Urine Desmosine as a Marker of Lung Injury in Spine Surgery

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Abstract The objective of this prospective observational study was to determine if urine desmosine levels, a marker of lung injury, increase in response to the perioperative insults of anterior and posterior spine surgery. Desmosine, a

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Each author certifies that his or her institution has approved the reporting of these cases, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participating in the study was obtained.

Level of Evidence: Level III. Prognostic study

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stable breakdown product of elastin, has been proposed as a surrogate marker of lung injury in patients with COPD, tobacco use, and ARDS. We recently evaluated this marker in patients undergoing knee surgery, but the utility of desmosine as a marker of lung injury in patients undergoing spine surgery remains unstudied. In this study, we enrolled ten consecutive patients, who underwent anterior/posterior spine surgery. Patient demographics and perioperative data were recorded. Urine samples were collected at baseline, 1 day, and 3 days postoperatively and analyzed for levels of desmosine using a previously validated radioimmunoassay. Desmosine levels were 35.9 ± 18.2 pmol/mg creatinine at baseline, 38.7 ± 11 pmol/mg creatinine on postoperative day 1, and 70.5 ± 49.1 pmol/mg creatinine on postoperative day 3, respectively. Desmosine/creatinine ratios measured on day 3 postoperatively were significantly elevated compared to levels at baseline, and represented a 96.3% increase. No difference was seen between levels at baseline and day 1 postoperatively. In conclusion, we were able to show a significant increase in urine desmosine levels associated with anterior/posterior spine surgery. In the context of previous studies, our findings suggest that desmosine may be a marker of lung injury in this setting. However, further research is warranted for validation and correlation of desmosine levels to clinical markers and various degrees of lung injury.

Keywords urine desmosine · spine · surgery · lung injury · biomarkers · perioperative

Introduction

Lung injury after sequential anterior and posterior spine surgery may occur secondary to perisurgical insults [1]. However, it is difficult to quantify and the relatively low incidence of clinical ARDS makes it difficult to study in clinical trials. Researchers have resorted to surrogate indicators in the past to quantify the problem, including the measurement of pulmonary vascular resistance [1] and radiographic imaging techniques [2], but these methods are

burdened by their invasiveness and/or non-specificity. Biomarkers of subclinical lung injury, such as cytokines and inflammatory cells in bronchoalveolar fluid, have also been employed, but are often cumbersome to obtain and analyze [3].

Desmosine, a unique and stable breakdown product of elastin that is easily measurable in urine [4], has been proposed as a surrogate marker of lung injury in patients with cystic fibrosis [5], chronic obstructive pulmonary disease [6], and tobacco use [7] and elevated levels have recently been linked to increased mortality in ARDS patients [8]. The utility of desmosine as a marker of lung injury in surgical patients, and especially patients undergoing spine procedures, however, remains largely unstudied [9]. In order to determine its utility in this setting, we investigated if desmosine levels would increase in response to the perioperative insults in spine surgery patients undergoing sequential anterior and posterior procedures.

Methods

After approval by the institutional review board we obtained written consent from ten consecutive patients, who underwent sequential anterior and posterior spine surgery and had no history of renal failure. All ten patients completed the study. There were four male and six female patients. The average age was 49.7 years and the average BMI was 27.1. Nine patients were ASA class II and one was ASA class III (Table 1). The indication for surgery was degenerative disk disease in $n=1$, spinal stenosis in $n=2$, pseudoarthrosis in $n=2$, scoliosis in $n=1$, and spondylolisthesis in $n=4$ of cases, respectively. The average number of levels of instrumentation was 2.4 (range 1–6). Three of the ten patients had previous spine surgery. No procedures required an intrathoracic approach. Only one patient had pre-existing pulmonary disease in the form of sarcoidosis.

Anesthesia was induced with intravenous injection of midazolam 5 mg, fentanyl 250 µg, propofol 2 mg/kg, and vecuronium 0.1 mg/kg. After intubation and placement of central and arterial lines, anesthesia was maintained with isoflurane 0.25–0.5%, nitrous oxide 50% in oxygen/air, continuous infusion of propofol 100 µg/kg/min, fentanyl 1.5 µg/kg/h, and ketamine 0.15 mg/kg/h. Intermittent doses of intravenous vecuronium were administered as necessary. The patients were ventilated using volume-controlled minute ventilation, at an inspired oxygen fraction of 0.40, inspiratory-to-expiratory ratio of 1:2, and a respiratory rate adjusted to achieve normocapnia (ETCO₂ between 30 and 36 mmHg). Tidal volumes were between 8 and 10 ml/kg of ideal body weight, not to exceed peak airway pressures of 30 cm H₂O. Positive end expiratory pressure of 5 cm H₂O was applied.

After induction of anesthesia, positioning on a four-poster-frame and sterile preparation of the surgical site, routine subperiosteal exposure of the vertebral levels involved was achieved for the posterior portion of the operation. Decompression and stabilization with the use of segmental spinal pedicular instrumentation procedures were performed

Table 1 Patient demographics

Patient demographics	
Male/female	4M/6F
Age (years)	49.7±13.1
Height (cm)	168.5±7.8
Weight (kg)	77.6±7.8
BMI (kg/m ²)	27.1±2.2
Creatinine (mg/dl)	0.8±0.22
ASA classification II/III	9 (II)/1(III)
Surgical time (minutes)	467±167

Data are presented as mean and standard deviation

ASA American Society of Anesthesiologists, BMI body mass index, F female, M male

as indicated according to each patient's needs. For the anterior portion of the procedure patients were positioned laterally or supine depending on the segments of operation. Incision was either in the flank or paramedian. The spine was exposed using a retroperitoneal approach. The psoas muscle was identified and retracted laterally to expose the anterior and lateral aspect of the spine. The segmental lumbar vessels were ligated if required. The great vessels were gently retracted to access the anterior aspects of the disk spaces. After a thorough discectomy, cages were inserted in the disk spaces for fusion. Red blood cell salvage equipment was utilized as per routine.

Urine samples were collected at baseline, 1 day, and 3 days postoperatively and 100 µl analyzed for levels of desmosine using a previously validated radioimmunoassay [4, 10, 11]. Concomitant analysis of urine creatinine levels was performed to adjust for dilution as previously described [8]. Results are presented as picomoles of desmosine per milligram of creatinine.

We modeled the relationship of the desmosine level as a function of time (baseline, postoperative day1, and postoperative day3 using linear regression with inference based on the generalized estimating equations method) [12]. Changes in urine desmosine levels over time are detected using appropriate linear contrasts. A P value of <0.05 was considered significant.

Results

Urine desmosine is increased after spine surgery and reaches a peak level on POD#3 ($p=0.02$). Average (±standard deviation) desmosine levels were 35.9±18.2 pmol/mg creatinine at baseline, 38.7±11.0 pmol/mg creatinine on postoperative day1, and 70.5±49.1 pmol/mg creatinine on postoperative day3, respectively. Desmosine/creatinine ratios measured on day3 postoperatively were significantly elevated compared to levels at baseline and postoperative day1, and represented a 96.3% and 88.5% increase ($p=0.02$), respectively. No difference was seen between levels at baseline and day1 postoperatively (7.8% increase, $p=0.51$). The data trends for individual patients supported the overall kinetic findings of our study (Fig. 1). Intraoperative fluid balance was representative of that encountered during anterior and posterior spine surgery (Table 2).

Fig. 1. Absolute urine desmosine/creatinine (pmol/mg) trends for individual patients over time

Of note, the patient with the largest increase in desmosine levels (44 pmol desmosine/mg creatinine at baseline to 211.5 pmol desmosine/mg creatinine on day3 postoperatively; Fig. 1), required prolonged postoperative ventilation beyond the first postoperative day and exhibited clinical signs of acute lung injury. All other patients were extubated within 1 day after surgery. In order to eliminate outlier bias, data were analyzed without samples contributed from the patient exhibiting lung injury. However, this did not significantly change our findings and conclusions regarding the kinetics of urine desmosine levels.

Discussion

In this pilot study, we were able to identify a significant increase in urine desmosine levels associated with sequential anterior and posterior spine surgery. A significant average increase of 96.3% from baseline was found on postoperative day3. The highest levels of urine desmosine were found in a patient who developed clinical signs of lung injury and required prolonged mechanical ventilation.

Our study is limited by a number of factors. As a pilot project, the number of patients enrolled is small and larger studies are needed to confirm our findings. Furthermore, the specificity of desmosine as a marker of lung catabolism may be questioned as it may originate from other sources of elastin in the body, i.e., ligaments. However, although elastin is not exclusive to pulmonary tissue, the extracellular

matrix of the lung is a major source of this protein and in the absence of injury is stable over a person's lifetime [4, 8, 10, 13, 14]. Furthermore, the majority of ligaments, the most likely source of extrapulmonary elastin during spine surgery, are removed intraoperatively, thus eliminating this structure as a major source of desmosine that would result from postoperative ligament catabolism.

During lung injury, elastin breakdown takes place secondary to exposure to proteases from neutrophils and macrophages [13]. Among the breakdown products are the crosslinks desmosine and isodesmosine, which are unique to elastin, are extremely stable and are excreted via renal elimination in the urine [13]. Animal studies have shown that after rapid release into the bloodstream desmosine sequesters in the kidney tissue followed by slow release into the urine [15]. These kinetic data may in part explain the peak in desmosine levels on day3 in our study. Furthermore, this finding may mirror delayed breakdown of elastin after the initial insult to the lung. Similar kinetics were found in a previous study of ARDS patients [8].

Previous studies involving non-surgical patients have established desmosine as a marker of lung injury [4–7], but the utility of this molecule as a marker of elastin catabolism as a result of surgery has not been studied in detail. In a preliminary analysis of desmosine levels in ten uni- and ten bilateral total knee arthroplasty patients, we were able to show significant increases in urine desmosine levels after bilateral but not unilateral procedures, suggesting that the size of embolic load may play a role in the level of lung injury observed [9]. Although a large portion of the elastin in the human body is found in the lung, the contribution of other sources, such as ligaments injured during surgery is unknown. With current methods it is not possible to distinguish desmosine origination from various body sources. Despite this limitation, there are a number of points supporting the utility of urine desmosine as a marker of lung injury during spine surgery.

Firstly, it is well established that significant lung injury does occur during anterior/posterior spine surgery [1–3, 16]. While the exact mechanism of lung injury associated with sequential anterior and posterior spine surgery remains unclear and is likely multifactorial, Urban et al. [2] was able to demonstrate an adverse pulmonary effect of perioperative

Table 2 Intraoperative fluid data

Intraoperative fluids (ml)	
Estimated blood loss	1,345±1,230
Crystalloid	5,070±1,883
Albumin 5%	525±448
Cell sever blood	289±451
Banked blood	330±440

Data are presented as mean and standard deviation

events in the form of an increase in pulmonary vascular resistance in 15% (8/55) of patients, usually during or after posterior instrumentation. In a follow-up study, the same author analyzed bronchoalveolar specimens and linked the presence of lipid-laden macrophages to possible embolization of fat and debris entering the bloodstream during the surgical procedure. This mechanism of lung injury is supported by echocardiographic studies, in which 80% of spine surgery patients experienced moderate to severe embolic events during instrumentation of the spine [13]. Roentgenographic abnormalities of the lung can be found in 64% of patients undergoing anterior and posterior spine surgery [3]. Additional insults include ventilator and blood product transfusion related factors, and likely contribute to the pulmonary damage.

In addition, we were able to clinically correlate increased desmosine levels in our study. The patient with the highest urine desmosine/creatinine ratio developed clinical signs of lung injury requiring mechanical ventilation beyond the first postoperative day. This patient had a prolonged surgery of approximately 13 h, during which he lost an estimated 1.3 l of blood. He required 2 U of packed red blood cells, 1 l of albumin, 500 ml of cell saver blood, and 6 l of crystalloid. His postoperative chest radiograph was consistent with pulmonary edema and he remained intubated until postoperative day 2 requiring only supportive care. He was discharged to the ward on postoperative day 4. It is likely that the reason for this patient's pulmonary pathology was multifactorial and included surgical, ventilator- and transfusion-related insults.

In conclusion, we were able to identify a significant increase in urine desmosine levels associated with sequential anterior and posterior spine surgery. In the context of previous studies, our findings suggest that desmosine may be a marker of lung injury in this setting and in addition to other markers could be used to study this entity. However, at this point, the value of urine desmosine as a marker of lung injury may be highest in qualitative, comparative studies targeted to evaluate specific lung protective interventions, thus largely negating the aforementioned limitations of specificity. Further research is warranted for validation and correlation of desmosine levels to clinical markers and various degrees of lung injury.

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