ORIGINAL ARTICLE

Role of plasma ammonia level in detecting intra-abdominal hemorrhage following blunt abdominal trauma

Davood Farsi, Ali Akbar Khademi Fadaki[1], Nahid Kianmehr[2], Saeed Abbasi, Mahdi Rezai, Mohammad Marashi, Mani Mofidi

Department of Emergency Medicine, Iran University of Medical Sciences, Tehran, [1]Department of Emergency Medicine, Mashad University of Medical Sciences, Mashad, [2]Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran

Background: Blunt abdominal injury is a leading cause of death in trauma patients. A reliable test predicting intra-abdominal hemorrhage would be a novel method. The study objective was to assess the diagnostic accuracy of plasma ammonia in detection of intra-abdominal bleeding in patients with blunt abdominal trauma (BAT). **Materials and Methods:** In this observational study, all patients suffering from BAT, referred to our university teaching hospital included. The levels of ammonia were measured at the time of emergency department admission and 1 h after initial treatment. Demographic data, vital signs, and venous blood gas reports were recorded. Findings of contrast-enhanced abdominopelvic computed tomography scan and laparotomy were assumed as a gold standard for abdominal injuries. **Results:** A total of 104 patients was enrolled in the study. 15 patients (14.4%) had intra-abdominal hemorrhage and the mean plasma ammonia level in this group was significantly higher than the other patients on admission time (101.73 ± 5.41 μg/dL vs. 47.36 ± 26.31 μg/dL, $P < 0.001$). On receiver-operator characteristic curve analysis, in cutoff point of 89 μg/dL, the sensitivity, specificity, positive and negative likelihood ratios were 100% (95% confidence interval [CI], 79.6-100), 93.26% (95% CI, 86-96.8), 14.83 (95% CI, 6.84-32.12), and 0, respectively. **Conclusion:** The study findings suggest the measurement of ammonia level at the time of admission in the patients with BAT would be a useful test predicting intra-abdominal hemorrhage. Furthermore, decrease in the ammonia level could be a useful marker for monitoring response to treatment in these patients.

Key words: Bl1unt abdominal trauma, intra-abdominal hemorrhage, plasma ammonia level

How to cite this article: Farsi D, Fadaki AAK, Kianmehr N, Abbasi S, Rezai M, Marashi M, Mofidi M. Role of plasma ammonia level in detecting intra-abdominal hemorrhage following blunt abdominal trauma. J Res Med Sci 2014;19:1080-5.

INTRODUCTION

Blunt abdominal trauma (BAT) is one of the most considerable causes of injury in trauma patients.[1] A survey on 1,224 trauma patients admitted to Liverpool hospital reported that 79% of them had BAT, and the main causes were road accidents.[2] Stable patients who suffering from BAT may have intra-abdominal hemorrhage. Some of them need surgical intervention due to solid or hollow organs injuries.[3] In multiple trauma patients, symptoms and signs of peritoneal irritation might be unreliable for diagnosis of intra-abdominal injury. Hence, laboratory data can be useful to help doctors in this difficulty.[4]

Laboratory tests (complete blood count, venous blood gas, base deficit, and urinalysis), diagnostic peritoneal lavage, and imaging (computed tomography [CT] scan and sonography) are frequently used in evaluating trauma patients. They have some limitations such as lack of enough sensitivity or specificity, unavailability in some medical centers, and impossibility for few patients.[5-11] Finding a fast and accurate test to predict intra-abdominal hemorrhage would be so conductive and time-saving.

Based on few clinical studies, admission high ammonia levels in trauma patients may suggest abdominal hemorrhage.[12,13]

Considering the measurement of plasma ammonia is an available and very fast test, also there is no high quality evidence in this topic; this study was designed to investigate diagnostic precision of plasma ammonia in detection of intra-abdominal hemorrhage among patients suffering from BAT.

MATERIALS AND METHODS

This survey was performed as a prospective observational study. In a period of 6 months from September 2010 to February 2011, all patients presented to the emergency

Address for correspondence: Dr. Mani Mofidi, Department of Emergency, Iran University of Medical Sciences, Sattarkhan Ave., Nyaiesh St., Rasoul Akram Complex, Tehran, Iran. E-mail: m-mofidi@sina.tums.ac.ir
Received: 27-11-2013; **Revised:** 15-06-2014; **Accepted:** 23-09-2014

department of our university teaching hospital with BAT enrolled in the study. The study was approved by the human subjects committee at our department. The code number of the research project in Iran University of Medical Sciences was 907. The patients with cardio-respiratory arrest, penetrating trauma, liver and kidney disease, other injuries that would lead to significant hemorrhage, patients who received prehospital intravenous (IV) fluid or blood components before sampling (because early IV hydration could change the value of plasma ammonia in our patients) and the period time more than 1 h between trauma and blood sampling (because we wanted to evaluate plasma ammonia as an early predictive test in BAT. Furthermore, the half-life of plasma ammonia is relatively short) were excluded.

According to inclusion criteria, 104 of 136 patients with BAT were recruited. At our center, trauma patients are treated according to the American College of Surgeons' Advanced Trauma Life Support protocol.[14] Demographic data, vital signs including shock index (SI) (heart rate/systolic blood pressure) at admission, venous blood gas reports, findings of abdominal sonography, and need for blood transfusion were recorded. The SI is normally 0.5-0.7 and has been shown to be elevated in the setting of acute hypovolemia and left ventricular dysfunction.[15] In this study, the indices higher than 0.7 assumed high SI. Findings of contrast-enhanced abdominopelvic CT scan and laparotomy considered as standard criteria for determining abdominal injuries (hemorrhage). Levels of ammonia measured at arrival time to the ED and 1 h after therapeutic interventions (fluid therapy, blood transfusion or at the end of laparotomy). Venous blood samples (3 ml) gathered in tubes filled with ethylene diamine tetra acetic acid. In order to maintain the cold chain, samples were quickly delivered to the laboratory, separation of plasma was done immediately, and then plasma ammonia level was measured within 10 min using spectrophotometer in 340 nanometers. Plasma ammonia was measured by an enzymatic method using glutamate dehydrogenase (normal range, 15-90 μg/dL) (Cobas Ammonia NH3L, Roche Diagnostics, Inc., Tokyo).[16] One week later, patients who discharged from ED after observation time were followed by telephone call about any abdominal problems.

All statistical analyses were performed using SPSS statistical software, version 18.0, IBM, Chicago, Illinois, USA. Since the data were normally distributed, parametric statistical tests were used. We analyzed continuous variables using independent (unpaired) *t*-test. The paired *t*-test was applied to compare plasma ammonia level before and after initial treatment. One-way ANOVA test was used to compare the three groups of disposition state regard of levels of ammonia. A κ (kappa) statistic was calculated to assess the agreement between findings of sonography and CT scan of the participants. A 2-by-2 table was used to calculate the sensitivity, specificity, positive predictive value, and negative predictive value. $P < 0.05$ considered as significant. Performance of plasma ammonia level for detecting intra-abdominal hemorrhage at various cutoff values was evaluated by receiver-operator characteristic (ROC) curve.

RESULTS

In a period of 6 months, 104 patients enrolled in the study. The results of medical records are shown in Table 1.

The mean ammonia level in all patients was 55.20 ± 31.04 μg/dL. In 21 patients (20.2%), the level of plasma ammonia was higher than normal (normal range 15-90 μg/dL according to the manufacturer's instruction). Abdominopelvic CT scan and sonography were performed according to BAT guidelines.[14] 15 patients had abnormal findings. Results of sonography and CT scan were consistent ($\kappa = 0.844$, $P < 0.001$). Only in two patients, the findings were incompatible (false negative sonography). Diagram 1 shows the flow of patients through the study.

Nine of 15 victims who were hemodynamically unstable or their CT scan findings were abnormal delivered to the operation room. In 7 patients, hemoperitoneum or intra-abdominal organ injuries (liver or spleen) were found during laparotomy. Pelvic external fixation was performed for 2 other patients. Those 6 patients, who did not deliver to the operation room, were admitted to the ICU and discharged a few days later without surgical intervention. Overall, 8 patients needed blood transfusion.

Table 1: Demographic and clinical characteristics of patients

Variables	Result (%)
Age (year), mean±SD	36.65±12.48
Sex (male)	91 (87.5)
SBP (mmHg), mean±SD	117.13±11.33
DBP (mmHg), mean±SD	74.53±6.23
Pulse rate, mean±SD	83.64±0.72
SI, mean±SD	0.72±0.12
High SI	18 (17.3)
Ammonia, mean±SD	55.20±31.04
Base excess, mean±SD	−0.26±2.74
HCO_3, mean±SD	24.21±3.72
PCO_2 (mmHg), mean±SD	43.83±5.36
PH, mean±SD	7.35±0.05
Elevated ammonia	21 (20.1)
Free fluid in sonography	13 (12.5)
Abdominal injury in CT scan	14 (13.4)
Transfer to the operating room	9 (8.6)
Blood transfusion	8 (7.6)

SD = Standard deviation; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; CT = Computerized tomography; SI = Shock index

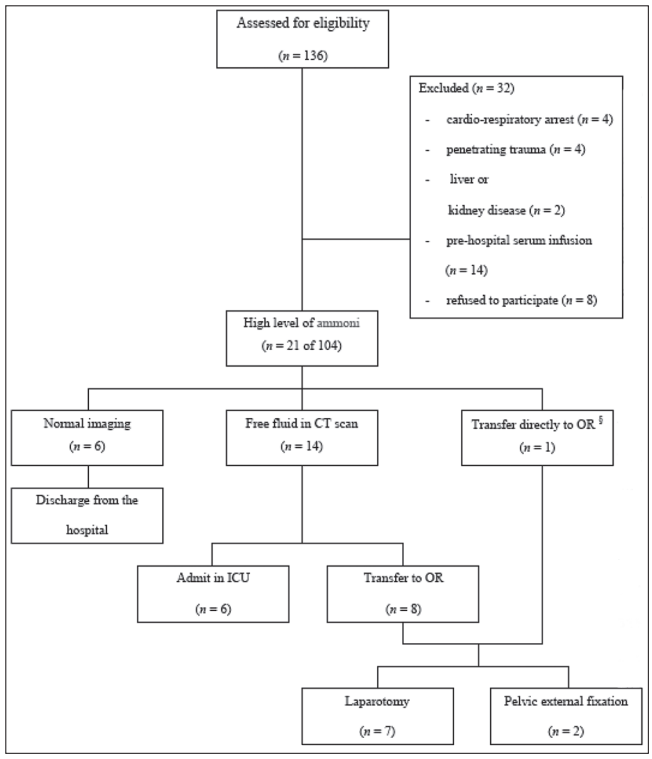


Diagram 1: Flow diagram of study participants

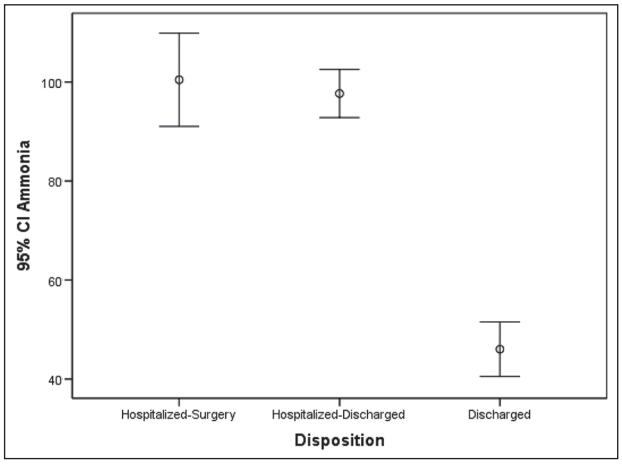
The mean level of plasma ammonia among patients with an abdominal injury was statistically higher than patients without injury (101.73 ± 5.41 μg/dL vs. 47.36 ± 26.31 μg/dL, independent *t*-test, $P < 0.001$) [Table 2]. Only 6 patients without abdominal injury had a high level of ammonia.

Statistical analysis showed a significant correlation between the level of ammonia and SI. In patients with the normal level of SI, the mean ammonia level was 50.28 ± 27.66 μg/dL. In patients with high level of SI, it was 78.72 ± 36.14 μg/dL (independent *t*-test, $P < 0.001$).

We found that the ammonia level was higher in patients who received transfusion than the others (105.33 ± 3.21 μg/dL vs. 53.71 ± 30.25 μg/dL, independent *t*-test, $P = 0.004$). Actually, in all patients who received transfusion the plasma ammonia levels were more than 90 μg/dL.

Regarding patients plasma ammonia level and outcome, we found that in patients who discharged from ED, the level of ammonia was statistically lower than hospitalized patients (one-way ANOVA, Tukey HSD, $P < 0.001$) [Graph 1].

Moreover, high ammonia level and abdominal free fluid were reported in two patients who died. Although this result was not statistically significant ($P > 0.05$), a larger study is required to ascertain if an association with the ammonia level and patients mortality exists.



Graph 1: The plasma ammonia level was markedly lower in patients discharged from ED than hospitalized ones

Table 2: Comparison of plasma ammonia level in certain categories of patients

Variable	Plasma ammonia level (μg/dL)		*P*
	+	–	
Intra-abdominal injury	101.73±5.41	47.36±26.31	<0.001
High Shock index	78.72±36.14	50.28±27.66	<0.001
PRBC transfusion	105.33±3.21	53.71±30.25	0.004
Male	55.93±30.82	50.08±33.39	0.527
Free fluid in US	96.87±16.68	48.18±27.17	<0.001

PRBC = Packed red blood cell; US = Ultrasound

We compared the ammonia level in two genders. It revealed that the level of ammonia in men and women was 55.9 and 50.1 μg/dL, respectively, without any significant difference (independent *t*-test, $P = 0.527$). There was no relation between the level of ammonia and age either (Pearson correlation, $P = 0.579$).

The results of abdominal CT scan and laparotomy were used as a gold standard for determination of the cutoff point (a patient was considered positive, when one of the noted variables were positive).

On ROC curve analysis, in cutoff point of 89 μg/dL, the sensitivity, specificity, positive and negative likelihood ratios were 100% (95% confidence interval [CI], 79.6-100), 93.26% (95% CI, 86-96.8), 14.83 (95% CI, 6.84-32.12), and 0, respectively. Performance of plasma ammonia level for detecting intra-abdominal hemorrhage at various cutoff values is shown in Table 3. As shown in Table 3, the optimal cutoff level of ammonia was 89 μg/dL. The area under curve (accuracy of the test) for plasma ammonia level was calculated 0.95 (95% CI, 0.91–0.99) [Graph 2]. Area under the curve for variables in ROC curve has been shown in Table 4.

One hour later, the level of ammonia was measured again in 15 patients with intra-abdominal bleeding after medical

Table 3: Performance of plasma ammonia level for detecting intra-abdominal hemorrhage at various cutoff values

Cutoff values	Sensitivity	Specificity
84.5	100	91
89	100	93.26
93.5	86.67	93.26
95.5	86.67	94.38
97.5	80	95.5

Table 4: Area under the curve for variables in ROC curve

Test result variable(s)	Area	SE[a]	Asymptotic significant[b]	Asymptotic 95% CI	
				Lower bound	Upper bound
Ammonia	0.958	0.020	0.000	0.918	0.997
SBP	0.053	0.025	0.000	0.005	0.102
HR	0.844	0.055	0.000	0.737	0.952
BE	0.127	0.058	0.000	0.013	0.240
SI	0.940	0.026	0.000	0.889	0.992

[a]Under the nonparametric assumption; [b]Null hypothesis: True area = 0.5; CI = Confidence interval; SE = Standard error; SBP = Systolic blood pressure; HR = Heart rate; SI = Shock index; ROC = Receiver-operator characteristic, BE = Base Excess

and surgical management and in 13 of them (86.6%) level of ammonia returned to the normal range (69.2 ± 11.6 μg/dL) (paired *t*-test, $P = 0.07$).

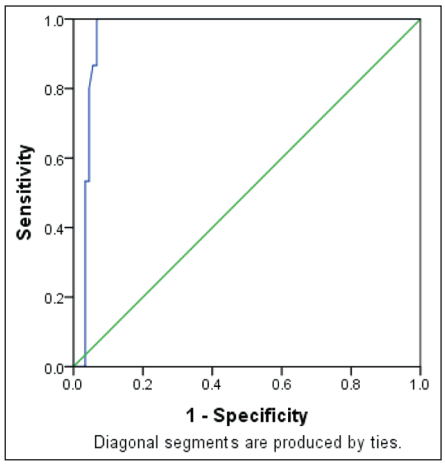
None of the discharged patients had abdominal complaint or death on 7th day of follow-up through telephone call.

DISCUSSION

We found that the high level of plasma ammonia in BAT patients could be a valuable predictor of intra-abdominal hemorrhage. During intra-abdominal hemorrhage, liver blood flow is decreased, and consequently liver function impairment occurs. This causes reducing glutamine production in peri-central hepatocytes and decrease urea production in peri-portal hepatocytes. Hence, ammonia excretion diminishes and its plasma level increases.[13,17]

This survey showed that plasma ammonia level is a worthy factor for detecting intra-abdominal hemorrhage in BAT. In those patients whom intra-abdominal bleeding proved by laparotomy or diagnostic interventions, higher plasma ammonia level was reported.

Hagiwara and Sakamoto[12] did the same study included 282 trauma patients in two groups, with and without intra-abdominal hemorrhage. The mean ammonia level in the first group was significantly higher, 113 ± 52.2 versus 55.4 ± 20.8 μg/dL. Sensitivity and specificity of plasma ammonia level in the diagnosis of intra-abdominal bleeding in blunt trauma patients were 82% and 89%, respectively. These results are a little different with ours. They chose the cut-off level of 77 μg/dL, but



Graph 2: Receiver operating characteristics (ROC) curve for plasma ammonia level for detecting intra-abdominal hemorrhage in blunt abdominal trauma with an area under the ROC curve = 0.958

we calculated 5 different cut off points. Besides, the number of patients in their study were more than the current study.

The other finding we reached was a significant correlation between plasma ammonia level and SI. Several studies showed that after reducing intravascular volume, SI increases.[18,19]

We also found a significant relation between plasma ammonia level and abnormal findings in CT scan or laparotomy. Hence, it is reasonable to have great consideration and perform appropriate emergency management for patients with BAT who have high ammonia level.

In our study, 8 patients received blood transfusion and in all of them level of plasma ammonia was higher than normal range. Hence, it may seem that there is a correlation between increased plasma ammonia level and need of blood transfusion.

Serum half-life of ammonia is a few minutes.[19] If plasma ammonia level remains high; it means the process of intra-abdominal injury is still continued. One hour after medical or surgical treatment, the level of ammonia measured again and in most of the patients returned to the normal range. Hence, we propose that there is a relation between change of plasma ammonia level and management quality and adequacy.

To the best of our knowledge, there is no study that measured the level of ammonia in trauma patients before and after treatment. In the other way, the present study is the first survey that shows plasma ammonia level decreases after medical or surgical interventions.

Limitations

This study suffers from some limitations. With respect to inclusion criteria, the plasma ammonia level is not a confident test. Patients who suffer from cardio-respiratory arrest, penetrating trauma, and some kind of hemorrhage like hemothorax or bleedings due to limb fractures may have false positive results.

87.5% of the patient population were male. This could be a limitation of this study because it may skew the results from a gender bias perspective.

The other one is the number of trauma patients with the end point we examined was small. Further studies with more patients could reach the more accurate findings.

We did not evaluate the relation between ammonia level and amount of intra-abdominal free fluid. Future studies could mention it.

There are currently more accurate ways to detect intra-abdominal hemorrhage like ultrasound and CT scan. Hence, the use of ammonia levels alone is an imprecise method of detecting bleeding. Whenever this imaging is not available, plasma ammonia level could be a useful test to find which blunt trauma patients have intra-abdominal injuries.

CONCLUSION

Physicians do not rely on laboratory values alone to diagnose intra-abdominal hemorrhage following BAT. Our study suggests that measurement of plasma ammonia level may be a valuable diagnostic factor for detecting intra-abdominal hemorrhage and can be used as a predictive test in these patients. Furthermore, decreasing the level of ammonia to the normal range may suggest a proper response to medical treatments in the patients. Future studies with a larger number of cases are needed to investigate about ammonia levels in addition to lactate and base deficits to evaluate efficacy of resuscitation in trauma patients with intra-abdominal hemorrhage.

ACKNOWLEDGMENTS

This research was residency thesis of Dr. Ali Akbar Khademi Fadaki by supervision of Dr. Mani Mofidi that has been supported by Iran University of Medical Sciences grant with research project number of 907.

AUTHOR'S CONTRIBUTION

MM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. K AA contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. FD, AS and MM contributed in revising the draft. KN contributed in the revising the draft and approval of the final version of the manuscript. MR did analysis and interpretation of data.

REFERENCES

1. Kendall JL, Kestler AM, Whitaker KT, Adkisson MM, Haukoos JS. Blunt abdominal trauma patients are at very low risk for intra-abdominal injury after emergency department observation. West J Emerg Med 2011;12:496-504.
2. Smith J, Caldwell E, D'Amours S, Jalaludin B, Sugrue M. Abdominal trauma: A disease in evolution. ANZ J Surg 2005;75:790-4.
3. Chen ZB, Zhang Y, Liang ZY, Zhang SY, Yu WQ, Gao Y, *et al.* Incidence of unexplained intra-abdominal free fluid in patients with blunt abdominal trauma. Hepatobiliary Pancreat Dis Int 2009;8:597-601.
4. Mofidi M, Hasani A, Kianmehr N. Determining the accuracy of base deficit in diagnosis of intra-abdominal injury in patients with blunt abdominal trauma. Am J Emerg Med 2010;28:933-6.
5. Lee WC, Kuo LC, Cheng YC, Chen CW, Lin YK, Lin TY, *et al.* Combination of white blood cell count with liver enzymes in the diagnosis of blunt liver laceration. Am J Emerg Med 2010;28:1024-9.
6. Diercks DB, Mehrotra A, Nazarian DJ, Promes SB, Decker WW, Fesmire FM, *et al.* Clinical policy: Critical issues in the evaluation of adult patients presenting to the emergency department with acute blunt abdominal trauma. Ann Emerg Med 2011;57:387-404.
7. Diamond IR, Hamilton PA, Garber AB, Tien HC, Chughtai T, Rizoli SB, *et al.* Extravasation of intravenous computed tomography scan contrast in blunt abdominal and pelvic trauma. J Trauma 2009;66:1102-7.
8. Holmes JF, Mao A, Awasthi S, McGahan JP, Wisner DH, Kuppermann N. Validation of a prediction rule for the identification of children with intra-abdominal injuries after blunt torso trauma. Ann Emerg Med 2009;54:528-33.
9. Patel NY, Riherd JM. Focused assessment with sonography for trauma: Methods, accuracy, and indications. Surg Clin North Am 2011;91:195-207.
10. Asadollahi S, de Steiger R, Gruen R, Richardson M. Management guideline in haemodynamically unstable patients with pelvic fractures: Outcomes and challenges. Emerg Med Australas 2010;22:556-64.
11. Paladino L, Sinert R, Wallace D, Anderson T, Yadav K, Zehtabchi S. The utility of base deficit and arterial lactate in differentiating major from minor injury in trauma patients with normal vital signs. Resuscitation 2008;77:363-8.
12. Hagiwara A, Sakamoto T. Clinical significance of plasma ammonia in patients with traumatic hemorrhage. J Trauma 2009;67:115-20.
13. Horsley JS 3rd, de Cosse JJ, Hood M, Sager N, Randall HT, Roberts KE. Elevation of blood ammonium in hemorrhagic shock. Ann Surg 1957;146:949-56.
14. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors. 8th ed. Chicago, IL: American College of Surgeons; 2008.
15. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. Am J Emerg Med 2005;23:323-6.
16. Balistreri WF, Rej R. Liver function. In: Burtis CA, Ashwood ER, editors. Tietz Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunders; 1996. p. 539-68.

17. Turner AJ, Whittle SR. Functions of aldehyde reductases. Biochem Soc Trans 1981;9:279-81.
18. Mizushima Y, Ueno M, Idoguchi K, Ishikawa K, Matsuok T. Is a shock index > 1 an adequate and clinically relevant recognition of hemorrhage shock? J Jpn Assoc Surg Trauma 2008;22:411-4.
19. Lockwood AH. Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis 2004;19:345-9.

Source of Support: Nil, **Conflict of Interest:** None declared.