Association of Serum Total Cholesterol Levels with Organ Failure and Onset of Infection in Trauma Patients

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Abstract

Background: Hypercholesterolemia occurs frequently in severely ill patients. Degree of hypercholesterolemia cumulative with the severity of injury may serve of prognostic significance.

Aim: To evaluate predictive abilities of serum cholesterol to detect the onset of infection, organ dysfunction, and clinical outcome in trauma patients.

Materials: Prospective cohort was performed on 111 trauma patients, average age 33.4±12.0 yrs for a period of six months (Jan-June 2012). Total cholesterol levels along with routine laboratory and clinical investigations were done on the day of admission with follow ups on 3rd, 5th & 7th day.

Results: Total 111 patients were included with average age of 33.4±12.0 years, 96 were males. Major site of trauma was head (45%), initial GCS was 11.1±4.4 and ISS was 13.1±5.8. 62% required mechanical ventilation. On admission cholesterol levels was 155.3±62.3 mg/dl, 48 hrs post admission was 152.3±57.6 mg/dl, day 3 was 156.0±61.7 mg/dl, day 5 was 163.3±65.6 mg/dl, and day 7 was 160.6±71.2 mg/dl. On admission cholesterol levels were significantly lower 139.7±61.5 mg/dl in patients who developed coagulopathy (p-value 0.03). Statistically insignificant differences in the cholesterol levels were observed in patients with/without organ failure 152.3±63.5mg/dl and 165.1±58.6 mg/dl respectively (p value 0.36); however cholesterol levels were low on admission and decreased throughout hospital stay for patients who developed infection and organ failure.

Conclusion: A progressive increment in cholesterol values was seen in convalescing patients. Cholesterol values at discharge were greater as compared to the admission values in survivors. A decline in cholesterol values throughout the course of hospital stay may indicate infection as lipoproteins participate in the immune system by binding and inactivating microorganisms and their toxic products; coagulopathy and in hospital mortality. Cholesterol may serve as a biologic marker for adverse outcomes in trauma patients.

Introduction

Massive injury leads to activation of the immune system and the early inflammatory immune response after trauma, therefore, degree of hypcholesterolemia often reflects severity of illness. In 1994 Dunham and coworkers [1] demonstrated that patients with severe trauma had a sudden reduction in total serum cholesterol concentration. Hypcholesterolemia has been found in patients undergoing surgical interventions [2], and in those with Multiple Organ Dysfunction Syndrome (MODS) [3-5] and burns [6]. Proposed explanations for the development of hypcholesterolemia include the acute phase response, down-regulation of hepatic synthesis, hemodilution from blood loss, dilutional effects with resuscitation, loss of apoproteins in burns [9]. Various studies have reported an association of hypcholesterolemia and increase mortality of critically ill patents [10,11] the poor prognosis of such low cholesterol concentrations has been documented in several epidemiological
studies [12-17]. Some studies also suggest the correlation of serum cholesterol with organ failure and sepsis [1, 18, 19].

Plasma lipoproteins (VLDL, LDL, Lipoprotein (a) and HDL) function primarily in lipid transport among tissues and organs. Since first suggested by Skarnes [21] that the lipoproteins also form complexes with microbial products, human studies have generally found that all lipoproteins participate in the nonspecific defense system. Lipoproteins function as part of a nonspecific immune defense system that binds and inactivates microbes and their toxins effectively by complex formation [22]. Lipoproteins can also detoxify Lipopolysaccharide (LPS) from Gram-negative bacteria and Lipoteichoic Acid (LTA) from Gram-positive bacteria, HDL being the most potent of these lipoproteins [23]. Infections can induce oxidation of LDL, and Oxidized LDL (OxLDL) in turn plays important anti-infective roles and protects against endotoxin-induced tissue damage [20].

Cholesterol and triglyceride levels reflect altered lipoprotein patterns, and often represent helpful adjunctive clinical tools. However, there are few studies defining the utilization of serum cholesterol as a biologic marker for infection and multiple organ dysfunction syndrome, and systemic inflammation.

Our aim was to assess the prognostic value of serum cholesterol to detect the onset of infection, organ/metabolic dysfunction, and clinical outcome of patients with various types and severities of injury, with the primary objective of determining the impact of trauma on serum cholesterol and its association with the onset of infection, organ dysfunction and mortality. Our secondary objective was to assess potential early risk factors of infection and organ dysfunction.

Materials & Methods

Study Design

Prospective cohort analyses of all trauma patients presented to the emergency department, and were triaged under red area i.e. patients that are of high priority and require immediate life-saving intervention were considered for the purpose of this study for the duration of six months (Jan-Jun 2012). Approval of the institute ethics committee was obtained prior to the commencement of the study.

The study group included patients of age group 16-65 yrs with either blunt or penetrating injuries, who are brought to the casualty within 24 hrs post trauma and requiring hospitalization of minimum 5 days. Patients with known history of tuberculosis, malaria or known infection or inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus at the time of admission were excluded from the study.

Laboratory investigations on admission, 3rd, 5th & 7th day were recorded on a structured proforma along with the clinical details.

Patients with hypotension, arrhythmia and those on vasopressors were considered to have cardiovascular dysfunction. Patients with the Aspartate Transaminase (AST) level >80 IU/L or serum bilirubin level >3 mg% were considered to have hepatic dysfunction. Central nervous system dysfunction was defined as patients with severe head injury, i.e. GCS <8. Pulmonary dysfunction was defined as the presence of bilateral lung infiltrate or Acute Respiratory Distress Syndrome (ARDS) or central venous pressure <18 mm Hg and mechanical ventilation. Patients with coagulopathy (PT/or aPTT ≥1.5×times the control) were considered to have hematologic dysfunction [24, 25].

Patients were first categorized based on the development of infection, then incidence of organ system dysfunction and lastly on the basis of in hospital mortality for further analysis. Early Ventricular Associated Pneumonia (VAP) occurs in the first-48 hours post injury, while late VAP takes place after the first-48 hours.

Study variables

Patient demographics, clinical and transfusion particulars i.e. patient age, gender, Injury Severity Score (ISS), Glasgow Coma Score (GCS), blood product transfusion, site and type of trauma (blunt or penetrating), presence of bone fracture, systolic BP, heart rate, sepsis, organ failure, coagulopathy, length of stay and in hospital mortality were recorded.

Laboratory investigation results i.e. complete blood counts (Hb, HCT & platelet count), coagulation assays (PT, aPTT & INR) and biochemistry analysis (liver function test, renal function test, electrolytes) along with total cholesterol estimation as per routine clinical practice were recorded.

Sample Collection and Processing

Routine blood samples were collected on admission, 3rd, 5th & 7th day for total cholesterol and other laboratory investigations. For biochemical analysis, 2 ml of venous blood was collected in a plain gel vial tube and serum was separated by centrifugation and analyzed using a fully automated Beckman Coulter Synchron CX9 biochemistry analyzer. Total Cholesterol was measured by a timed-end point method after enzymatic hydrolysis and oxidation.

Venous blood sample (2-ml) was collected in disposable Ethylene Di Amine Tetra Acetic Acid (EDTA) tubes, for estimation of basic hemogram parameters using a fully automated hematology analyzer, SysmexXE-2100. For estimation of blood gas 0.5 ml of arterial blood was withdrawn into a heparinized syringe from the radial or femoral artery, and analyzed on Combiline ABG analyzer.

Statistical analysis

The study patient group was categorized on the basis of onset of infection, incidence of organ failure and in hospital mor-
tality. The data was summarized as Mean±S.D. or Median (inter quartile range). The difference in the total cholesterol levels were compared between the categories by T-Test, followed by Analysis of Variance (ANOVA). A p-value of ≤0.05 was considered statistically significant.

Results

Subject characteristics

A total of 111 patients were included in the study group from Jan 2012-June 2012. Average age of the study group was about 33.4±12.0 years, with 96 males and 15 females. Head was the major site of trauma with 45% (50) patients, followed by orthopedic trauma with 17% (19) and polytrauma with 17% (19) [Figure 1].

FAST positivity was recorded for 16 patients; X-ray was performed for 12 patients. Average heart rate was 96.8±23.2 per min, systolic B.P was 120.9±23.0 mmHg. Incidence of bone fracture was observed to be 41.4% (46).

An initial average GCS of 11.1±4.4 and ISS of 13.1±5.8 were observed. Severity of head injury was severe (GCS<8) in 33.3% (37) and moderate in 15(13.5%) patients, where as the remaining 53.1% comprised of patients with mild (GCS14- 15) or no head injury. Severity of injury was high (ISS>16) in 35(31.5%) and low (ISS<16) in 76(68.4%) patients [Table 1].

### Parameters

| Parameters                       | Mean±SD     |
|----------------------------------|-------------|
| Age(years)                       | 33.4±12.0   |
| GCS                              | 11.1±4.4    |
| Severity of head injury#         |             |
| Severe                           | 37(33.3)    |
| Moderate                         | 15(13.5)    |
| Mild                             | 59(53.1)    |
| ISS                              | 13.1±5.8    |

| Severity of Injury#              | High(>16)   |
|----------------------------------|-------------|
|                                  | 35(31.5)    |
| Low (<16)                        | 76(68.4)    |

| Heart rate(per min)              | 96.8±23.2   |
| Systolic B.P(mmHg)               | 120.9±23.0  |
| Shock index                      | 0.8±0.2     |

| Transfusion requirements (units) | PRP(n=6)   |
|----------------------------------|------------|
|                                  | 3.5±0.8    |
|                                  | PRBC(n=26) |
|                                  | 2.9±1.4    |
|                                  | FFP(n=15)  |
|                                  | 3.8±1.6    |

| Cholesterol                      |             |
|----------------------------------|-------------|
| Day 1(n=111)                     | 155.3±62.3  |
| Day 2(n=111)                     | 152.3±57.6  |
| Day 3(n=110)                     | 156.0±61.7  |
| Day 5(n=104)                     | 163.3±65.6  |
| Day 7(n=90)                      | 160.6±71.2  |

| Triglycerides                     |             |
|-----------------------------------|-------------|
| Day 1(n=111)                      | 154.2(1-895)|
| Day 2(n=111)                      | 168.24(47-775)|
| Day 3(n=110)                      | 189.9(52-987)|
| Day 5(n=104)                      | 206.2(48-1336)|

| Hemoglobin                        | 11.7±2.2    |
| Total leukocyte count             | 13893.6±5753.2|
| Platelet                          | 189.9±92.9  |
| Total bilirubin                   | 1.0±0.4     |
| SGOT                              | 121.8(17-1399)|
| SGPT                              | 72.3(10-687)|
| Alkaline phosphatase              | 87.9±42.1   |
| Urea                              | 32.2±18.9   |
| Creatinine                        | 0.7±0.3     |
| Albumin                           | 3.6±1.1     |
| Glucose                           | 163.1±59.6  |
| INR                               | 1.3±0.4     |
| Fibrinogen                        | 283.0(60-1331)|
| PaO2(n=54)                        | 202.4(59.5-616)|
| Days of infection                 | 7.7(1-39)   |
| ICU stay(days)                    | 10(1-76)    |
| Fracture#                         | 46(41.4)    |
| Organ failure#                    | 85(76.5)    |
| Organ failure#                    | Single      |
|                                   | 40(36.0)    |
|                                   | multiple    |
|                                   | 45(40.5)    |
| Pulmonary failure#                | 68(61.2)    |
| Renal failure#                    | 11(9.9)     |

Figure 1: Site of Trauma.
Post Injury Cholesterol Levels

Average cholesterol levels on admission (n=111) was 155.3±62.3 mg/dl, on 48 hrs post admission (n=111) was 152.3±57.6 mg/dl, on follow up day 3 (n=110) was 156.0±61.7 mg/dl, day 5 (n=104) was 163.3±65.6 mg/dl, and on 7th day (n=90) was 160.6±71.2 mg/dl. On admission cholesterol levels were significantly lower 139.7±61.5 mg/dl in patients who developed coagulopathy, than patients who did not 165.2±61.2 (p-value 0.03) [Table 2].

| Study Outcome | Cholesterol 1 |
|---------------|---------------|
|               | mean±SD       | p value |
| Coagulopathy  | Yes(n=43)     | 139.7±61.5 | 0.03 |
|               | No(n=68)      | 165.2±61.2 |
| Organ failure | Yes(n=85)     | 152.3±63.5 | 0.36 |
|               | No (n=26)     | 165.1±58.6 |
| Renal failure | Yes(n=11)     | 158.4±16.9 | 0.88 |
|               | No (n=100)    | 155.0±63.2 |
| Hepatic failure| Yes(n=21)    | 153.3±65.4 | 0.87 |
|               | No (n=90)     | 155.8±61.9 |
| Pulmonary failure| Yes(n=68) | 155.9±63.1 | 0.9 |
|               | No (n=43)     | 154.3±61.7 |
| SOF/MOF       | Single(n=40)  | 156.9±63.2 | 0.54 |
|               | Multiple(n=45)| 148.2±64.1 |
| Infection     | Yes(n=51)     | 155.2±67.6 | 0.98 |
|               | No (n=60)     | 155.4±58.0 |
| VAP           | Early(n=48)   | 153.5±70.8 | 0.92 |
|               | Late (n=20)   | 153.1±52.8 |
| Mortality     | Yes (n=92)    | 154.7±62.0 | 0.96 |
|               | No (n=19)     | 155.4±62.7 |

Table 2: Association of on Admission Cholesterol Levels with the Study Outcomes.

There was an increase in cholesterol levels from 165.2±61.2 mg/dl at admission to 171.5±69.1 mg/dl on day 5 in patients who did not develop coagulopathy, whereas for patients who developed coagulopathy the cholesterol levels decreased from 139.7±61.5 mg/dl to 133.3±53.7 mg/dl within 48hrs of injury, the levels latter increased to 149±57.3 mg/dl by day 5. The patients were stratified based on their admission day cholesterol levels as Normal (150-200 mg/dl) (n=27), Very low (<100 mg/dl) (n=18), Low (100-150 mg/dl) (n=42) and High (>200mg/dl) (n=24) and compared with the study outcomes [Table 3].

| OUTCOMES       | Normal cholesterol | Very low cholesterol | Low cholesterol | High cholesterol | p value |
|----------------|---------------------|----------------------|-----------------|------------------|--------|
|                | (150-200)           | (<100)               | (100-150)       | (>200)           |        |
| Pulmonary failure| Yes(n=69)   | 18(26.0)              | 12(17.3)        | 23(33.3)         | 16(23.1)| 0.66  |
|                | No(n=42)             | 9(21.4)               | 6(14.2)         | 19(45.2)         | 8(19.0) | 0.69  |
| Hepatic failure | Yes(n=21)        | 3(14.2)               | 4(19.0)         | 9(42.8)          | 5(23.8) | 0.81  |
|                | No(n=90)             | 24(26.6)              | 14(15.5)        | 33(36.6)         | 19(21.1)| 0.92  |
| Renal failure  | Yes(n=11)           | 2(18.1)               | 1(9.0)          | 5(45.4)          | 3(27.2) | 0.02  |
|                | No(n=100)            | 25(25.0)              | 17(17.0)        | 37(37.0)         | 21(21.0) | 0.66  |
| Coagulopathy   | Yes(n=43)           | 6(13.9)               | 12(27.9)        | 17(39.5)         | 8(18.6) | 0.02  |
|                | No(n=68)             | 21(30.8)              | 6(8.8)          | 25(36.7)         | 16(23.5) | 0.66  |

Table 3: Association of admission day cholesterol levels with the Study Outcomes.
Organ failure | Yes(n=85) | 21(24.7) | 17(20.0) | 29(34.1) | 18(21.1) | 0.2  
| No(n=26) | 6(23.0) | 1(3.8) | 13(50.0) | 6(23.0) | 0.29  
| VAP | No(n=43) | 14(32.5) | 8(18.6) | 11(25.5) | 10(23.2) | 0.66  
| Early(n=48) | 7(14.5) | 7(14.5) | 24(50.0) | 10(20.8) | 0.95  
| Late(n=20) | 6(30.0) | 3(15.0) | 7(35.0) | 4(20.0) | 0.95  
| Infection | Yes(n=51) | 10(19.6) | 8(15.6) | 22(43.1) | 11(21.5) | 0.66  
| No(n=60) | 17(28.3) | 10(16.6) | 20(33.3) | 13(21.6) | 0.66  
| Mortality | Yes(n=19) | 4(24.3) | 3(15.7) | 7(36.8) | 5(26.3) | 0.66  
| No(n=92) | 23(25.0) | 15(16.3) | 35(38.0) | 19(20.6) | 0.66  

Table 3: Association of Outcomes with Categorized Cholesterol Levels.

Significant difference in the cholesterol levels of patients who did/did not develop coagulopathy was seen, 6(13.9) had normal 12(27.9) very low, 17(39.5) had low and 8(18.6) had high levels of on admission cholesterol (p value- 0.02) [Figure 2].

Relationship of cholesterol levels with organ failure

Incidence of organ failure was 76.5%, 23% had no organ failure [Figure3], 69 developed pulmonary failure, 11 developed renal failure, and 21 developed hepatic failure. Out of the 77% patients who developed organ failure, 38 had single organ system failure, 37 had two organ system failures, and six had three organ system failures.

Admission day cholesterol levels of patients who developed organ failure (143.3±118.5 mg/dl) was lower than the patients who did not (177.8±129.9 mg/dl), but not statistically significant. Similarly, statistically insignificant differences in the cholesterol levels were observed amongst three organ failure groups (without/ with single and with multiple) (p value 0.54); also amongst the patients who suffered from single/poly trauma (p value 0.12) [Table 2]. Cholesterol levels of 152.3±63.4 mg/dl decreased to 146.8±57.7 mg/dl48 hours post injury. Patients who had no organ failure an increase in the 48 hour total cholesterol level (170.2±54.5 mg/dl) for seen from the admission level (165.0±58.6 mg/dl)

Out of the patients who developed any organ system failure 17(20.0) had very low and 29(34.1) had low cholesterol level. Out of the patients who developed pulmonary failure, 17.3% had cholesterol levels <100 mg/dl and 33.3% had low cholesterol levels,
for renal failure group 45.4% had low and 9% had very low cholesterol levels and for hepatic failure group 42.8% had low and 19% had very low cholesterol levels, however this variance in cholesterol levels was not observed to be statistically significant [Table 3, Figure 3].

An injury severity score of more than 16, statistically correlated with the development of organ failure. Out of the 35 patients with high ISS, 94.2% developed organ failure and 5.7% did not. 47% of the patients who developed pulmonary dysfunction had an ISS of >16 (p value <0.001), similarly a significant correlation of ISS >16 was observed in the patients who developed hepatic failure. 9.5% with hepatic failure had high ISS (p value 0.01). Severity of head injury was found to be significantly associated with the development of organ failure, as 59.3% patients with mild head injury, 86.6% with moderate head injury and 100% patients with severe head injury developed organ failure during the course of their hospital stay (p value <0.001). Other risk factors for the development of post trauma organ failure were mechanical ventilation (p value <0.001), presence of brain injury (p value <0.001), transfusion of blood components (p value 0.002) and infection (p value 0.007) [Table 4].

| Risk factors       | Organ failure | Infection | Mortality |
|--------------------|---------------|-----------|-----------|
|                    | Yes (n=85)    | No (n=26) | p value   | Yes (n=51) | No (n=60) | p value | Yes (n=19) | No (n=92) | p value |
| GCS                |               |           |           |            |           |         |            |           |         |
| Mild (n=59)        | 35 (59.3)     | 24 (40.6) | <0.001    | 19 (32.2)  | 40 (67.8) | 0.006   | 4 (6.7)    | 55 (93.2) | 0.003   |
| Moderate (n=15)    | 13 (86.6)     | 2 (13.3)  |           | 8 (53.3)   | 7 (46.6)  |         | 3 (20.0)   | 12 (80.0) |         |
| Severe (n=37)      | 37 (100)      | 0 (0.0)   |           | 24 (64.8)  | 13 (35.1) |         | 12 (32.4)  | 26 (67.5) |         |
| ISS                |               |           |           |            |           |         |            |           |         |
| Low (n=76)         | 52 (68.4)     | 24 (31.5) | 0.003     | 34 (44.7)  | 42 (55.2) | 0.7     | 8 (10.5)   | 68 (89.4) | 0.007   |
| High (n=35)        | 33 (94.2)     | 2 (5.7)   |           | 17 (48.5)  | 18 (51.4) |         | 11 (31.4)  | 24 (68.5) |         |
| Mechanical         |               |           |           |            |           |         |            |           |         |
| ventilation        | Yes (n=63)    | 63 (100)  | <0.001    | 37 (58.7)  | 26 (41.2) | 0.002   | 18 (28.5)  | 45 (71.4) | <0.001  |
| No (n=48)          | 22 (45.8)     | 26 (54.1) |           | 14 (29.1)  | 34 (70.8) |         | 1 (2.0)    | 47 (97.9) |
| Blood pressure     |               |           |           |            |           |         |            |           |         |
| Normal (n=28)      | 19 (67.8)     | 9 (32.1)  | 0.45      | 14 (50.0)  | 14 (50.0) | 0.87    | 5 (17.8)   | 23 (82.1) |
| Low (n=39)         | 31 (79.4)     | 8 (20.5)  |           | 17 (43.5)  | 22 (56.4) |         | 5 (12.8)   | 34 (87.1) |
| High (n=44)        | 35 (79.5)     | 9 (20.4)  |           | 20 (45.4)  | 24 (54.5) |         | 9 (20.4)   | 35 (79.5) |
| Chest injury       |               |           |           |            |           |         |            |           |         |
| Yes (n=19)         | 16 (84.2)     | 3 (15.7)  | 0.38      | 6 (31.5)   | 13 (68.4) | 0.16    | 5 (26.3)   | 14 (73.6) |
| No (n=92)          | 69 (75.0)     | 23 (25.0) |           | 45 (48.9)  | 47 (51.0) |         | 14 (15.2)  | 78 (84.7) |
| Brain injury       |               |           |           |            |           |         |            |           |         |
| Yes (n=64)         | 60 (93.7)     | 4 (6.2)   | <0.001    | 34 (53.1)  | 30 (46.8) | 0.07    | 16 (25.0)  | 48 (75.0) |
| No (n=47)          | 25 (53.9)     | 22 (46.8) |           | 17 (36.1)  | 30 (63.8) | 3.63    | 3 (6.3)    | 44 (93.6) |
| Shock              |               |           |           |            |           |         |            |           |         |
| Yes (n=58)         | 42 (72.4)     | 16 (27.5) | 0.27      | 29 (50.0)  | 29 (50.0) | 0.37    | 7 (12.0)   | 51 (87.9) |
| No (n=53)          | 43 (81.1)     | 10 (18.8) |           | 24 (45.1)  | 31 (54.8) |         | 12 (22.6)  | 41 (77.3) |
| Fracture           |               |           |           |            |           |         |            |           |         |
| Yes (n=48)         | 35 (72.9)     | 13 (27.0) | 0.42      | 24 (50.0)  | 24 (50.0) | 0.45    | 8 (16.6)   | 40 (83.3) |
| No (n=63)          | 50 (79.3)     | 13 (20.6) |           | 27 (42.8)  | 36 (57.1) |         | 11 (17.4)  | 52 (82.5) |
| Transfusion        |               |           |           |            |           |         |            |           |         |
| Yes (n=31)         | 30 (96.7)     | 1 (3.2)   | 0.002     | 19 (61.2)  | 12 (38.7) | 0.04    | 10 (32.2)  | 21 (67.7) |
| No (n=80)          | 55 (68.7)     | 25 (31.2) |           | 32 (40.0)  | 48 (60.0) |         | 9 (11.2)   | 71 (88.7) |
| Infection          |               |           |           |            |           |         |            |           |         |
| Yes (n=51)         | 45 (88.2)     | 6 (11.7)  | 0.007     | ----       | ----      |         | 8 (15.6)   | 43 (84.3) |
| No (n=60)          | 40 (66.6)     | 20 (33.3) |           | ----       | ----      |         | 11 (18.3)  | 49 (81.6) |
| VAP                |               |           |           |            |           |         |            |           |         |
| Early (n=48)       | 36 (75.0)     | 12 (25.0) | ----      | ----       | ----      |         | 4 (8.3)    | 44 (91.6) |
| Late (n=20)        | 18 (90.0)     | 2 (10.0)  | ----      | ----       | ----      |         | 7 (35.0)   | 13 (65.0) |
| Organ failure      |               |           |           |            |           |         |            |           |         |
| Yes (n=85)         | ----          | ----      | ----      | ----       | ----      |         | 18 (22.3)  | 66 (77.6) |
| No (n=26)          | ----          | ----      | ----      | ----       | ----      |         | 0 (0.0)    | 26 (100.0) |

Values in the table are expressed as n (%) 

Table 4: Risk Factors for the Development of Organ Failure, Incidence of Infection and in-Hospital Mortality in Trauma Patients.
Relationship of Cholesterol Levels with Infection

Blood culture positivity was recorded in 17% (19) patients, 20.7% (23) were positive for urine culture and 38.7% (43) had positivity for tracheal cultures. Infection was observed in 51 (45.9) patients, by an average of seven days post admission [Table 1]. Cholesterol levels of 155.1±67.6 mg/dl decreased to 151.2±60.7 mg/dl 48 hours post injury, with an average day of incidence of infection of 7.2 days. Patients without infection showed an increase in the total cholesterol level on day 7 (163.3±54.8 mg/dl) from the admission level (155.4±58.0 mg/dl). Early onset of ventilator associated pneumonia was observed in 43.2% (48) and in 18% (20) VAP developed 48 hrs post injury. Incidence of VAP was observed to significantly correlate with shock (p value <0.001). Out of the 58 patients who presented with shock 60.3% developed early VAP, 15.5 developed late VAP and 24.1 did not develop VAP.

94.4% of the patients with very low and 69% patients with low cholesterol levels developed organ failure. 38.9% of the patients with very low and 57.1% patients with low cholesterol levels developed late VAP. 16.7% of the patients with very low and 16.7% patients with low cholesterol levels developed early VAP. 44.4% of the patients with very low and 52.4% patients with low cholesterol levels developed organ failure [Table 3, Figure 3]. Severity of head injury, mechanical ventilation, and transfusion of blood product were observed to be risk factors for infection. Out of the 37 patients with severe head injury 64.8% developed infection, where as 35.1% did not (p value 0.006). 63 patients required ventilator associated breathing, of which 58.7% did and 41.2% did not develop infection (p value 0.002) [Table 4].

Relationship of cholesterol levels with mortality

A Mortality rate of 17% (19) was observed, 57.8% had an ISS of >16 (p value 0.007); on admission cholesterol level of patients who survived was 154.7±62.0 mg/dl and for those who did not survive was 155.4±62.7 mg/dl [Table 2]. On admission triglyceride of survivors was 146.4±94.9 mg/dl, and for non-survivors was 152.4±126.8 mg/dl. Ten non-survivors had on admission hypocholesterolemia, and 19 had low triglyceride levels.

For survivors an increase for the admission day cholesterol level of 155.4±62.7 mg/dl to 161.2±67.8 mg/dl on day 7 and for non-survivors a decrease from 154.7±62.0 mg/dl on admission to 145.3±61.5 mg/dl on day 5 was observed. Severity of injury (ISS>16), head injury, need for mechanical ventilation, transfusion of blood products and development of organ failure were learned to be statistically significant risk factors for in-hospital mortality in trauma patients [Table 4].

Discussion

Literature depicts that traumatic patient are seldom subjected to inflammatory responses apropos their condition. Decreased concentrations of total cholesterol, lipoproteins, and lipoprotein cholesterols are observed early in the course of critical illness. Infection and inflammation induce an Acute-Phase Response (APR), with multiple alterations in lipid and lipoprotein metabolism. VLDL concentrations are increased whereas LDL is either unchanged or decreased and HDL is decreased [22]. A few recent studies have shown that inflammation may be associated to a reduction in cholesterol level and increase in mortality. Their results indicated that serum cholesterol levels may serve as prognostic markers for outcome in trauma patients [26,27].

Hudgins et al demonstrated that high molecular weight lipoproteins not only bind LPS, but lipoproteins disappear from the general circulation in infected human beings [28]. They injected a small dose of LPS in normal volunteers and demonstrated the expected rise of the usual inflammatory markers and a fall of total cholesterol. Decreased synthesis of cholesterol precursors is the major cause of hypocholesterolemia in patients with multiple trauma [29]. Cholesterol during the first week after injury has been inversely associated with the number of ventilator days and hospital duration of stay [30].

The present study was conducted to assess the relationship of post trauma hypocholesterolemia with the development of infection, organ failure and in hospital mortality. A decrease in the cholesterol level was seen within 48 hrs of injury, with an incidence of organ failure of 76.5%, coagulopathy of 38.7% and infection of 45.9%. Cholesterol levels gradually increased in convalescing patients where as a further decrease was observed in patients who died during the course of their hospital stay; congruent results were reported by Dunham et al.26 studied 28 mechanically ventilated trauma patients, finding lower serum cholesterol concentrations in non-survivors, for the patients who survived, cholesterol at surgical ICU discharge was significantly increased (143±35mg/dl) compared with admission cholesterol 112±37mg/dl, in the present study admission day cholesterol 155.5±62.7 mg/dl which increased to 163.0±61.9 mg/dl on day 5.

D. Memis et al. studied 96 patients with diagnosed sepsis to evaluate cholesterol as a prognostic factor for survival. Cholesterol levels in non-survivors were significantly lower than those among survivors on day 1, day 2, and last day (P=0.001, P=0.001, and P = 0.010, respectively). The optimal cutoff points for cholesterol on day 1, day 2 and last day was ≤120 mg/dl, ≤123 mg/dl, ≤125 mg/dl, respectively. They concluded that cholesterol is a predictor of survival in patients with severe sepsis. Low cholesterol levels appear as a valuable tool for individual risk assessment and for stratification of high-risk patients in future intervention trials [31].

In surgical patients, Pacelli et al. retrospectively identified hypocholesterolemia as an independent predictor of mortality among 604 patients with intra-abdominal infection [32], and Gu et al. associated low total cholesterol concentrations with death in critically ill surgical patients[33]. Several studies highlight the relationship between low serum cholesterol and sepsis [27,34-35].

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Dunham et al.36 also studied 48-hour total Blood Cholesterol (BC) and other potential risk factors for the development of Ventilator-Associated Pneumonia (VAP). Their retrospective analysis concluded hypocholesterolemia is greater with chest injury, shock, and RBC transfusion, but less with brain injury, contradictory in the present study these associations were not observed.

Gordon37 studied patients with infection, to assess the correlation of the severity of infection and hypocholesterolemia, reported an association of low levels of admission serum cholesterol with higher APACHE III, Multi-Organ Dysfunction Score, longer length of stay, and higher mortality in a surgical ICU setup. There is growing evidence that hypocholesterolemia is a manifestation of systemic inflammatory up-regulation [26,37]. Hypocholesterolemia has also been associated with the development of nosocomial infections, especially in the postoperative period [38-40].

Hypocholesterolemia during infection is multifactorial; decrease lipoprotein synthesis due to hepatocytes exposure to TNF and IL-641 is accompanied by an increase in oxidation of LDL-cholesterol [42]. Since LDL participates in the immune system, high plasma cholesterol concentrations suggest survival, not a risk. There is published evidence that high cholesterol is protective against infectious diseases. Plasma cholesterol levels have been found to be inversely associated with total mortality in the elderly and with mortality from respiratory and gastrointestinal diseases, most of which have an infectious origin[43]. Cholesterol levels are also inversely associated with mortality after post-operative abdominal infections, inversely associated with the risk of being admitted to hospital because of an infectious disease.

Statistically significant variation in the levels of cholesterol in patients who did and who did not developed coagulopathy was observed in the study. Direct relationships between cholesterol, prothrombin activity and fibrinogen have recently been reported by Giovannini et al [44], who studied the correlations between albumin, other plasma proteins, additional variables and clinical events in liver resection patients. The considerable changes in the plasma lipid pattern following severe trauma suggest the presence of an abnormal lipoprotein with increased affinity to fibrin, thereby inhibiting fibrinolysis. This might well be a pathogenic mechanism in the development of post-traumatic respiratory distress syndrome [45]. Inflammatory responses are almost invariably accompanied by alterations of the coagulation system. Activation of coagulation and down regulation of anticoagulant systems and fibrinolysis occurring adjacent to inflammation results in coagulopathy.

The hemostatic dysfunction in infection, characterized by the excessive activation of procoagulant pathways and the impairment of anticoagulant activity, leads to disseminated intravascular coagulation and results in microvascular thrombosis, tissue hypoperfusion and, ultimately, multiple organ failure and death. The limitation of this study is that only total cholesterol and triglyceride levels were assessed, and its components such as LDL, HDL were not estimated, also that some cases were lost due to follow up.

Conclusion

Cholesterol values increased from the on-admission levels in the convalescing patients. In the survivors the cholesterol values at discharge were greater as compared to the admission values. On admission hypocholesterolemia was observed in ten non-survivors and 19 had low triglyceride levels. As inflammatory response is inseparable from the coagulation process, coagulation disorders, therefore significant association of hypocholesterolemia and coagulopathy have been observed in the present study.

A progressive decrement in cholesterol values or no increase in the on-admission values may indicate infection, coagulopathy and in-hospital mortality. Lipoproteins participate in the immune system by binding and inactivating microorganisms and their toxic products, which may explain our result. Cholesterol values may serve as a biologic marker for infection and multiple organ dysfunction syndrome, and systemic inflammation. Repeated cholesterol determinations may have a prognostic implication and help to identify patients who may require more aggressive management to avoid complications.

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