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Assessment of surgical risk factors in the development of ventilator-associated pneumonia in neurosurgical intensive care unit patients: Alarming observations

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Abstract:

Background: Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in patients receiving mechanical ventilation (MV) and contributes to a longer intensive care unit (ICU) stay, duration of MV, and a high morbidity and mortality.

Objective: The purpose of study was to determine the incidence of VAP in neurosurgery ICU patients and to assess the probable contributing neurosurgical risk factors like the site and nature of the lesion in the brain, the duration of surgery, blood loss during surgery, and infection elsewhere in the body, in the development of VAP.

Materials and Methods: The prospective clinical study included patients with a Glasgow Coma Scale (GCS) score>8 undergoing a neurosurgical procedure and postoperatively receiving MV for >48 hours, who were followed for the development of VAP. The diagnosis of VAP was in accordance with the Centers for Disease control (CDC) guidelines and was confirmed with a positive quantitative culture in the endotracheal tube aspirate samples.

Results: The incidence of VAP in our study was 70%. Aneurysmal subarachnoid hemorrhage (SAH) [Grade 3, 4 and 5] was the most common underlying condition followed by posterior fossa surgery, and surgery of the craniovertebral junction and cervical spine. Patients with a supratentorial compartment etiology had a slightly higher incidence (53%) of VAP as compared to the infratentorial compartment one. Patients with significant intraoperative blood loss and receiving blood transfusion had a higher incidence of pulmonary complications. *Acinetobacter baumannii* was the most common pathogen isolated followed by *Pseudomonas aeruginosa*, with high resistance trends being prevalent among the commonly used antibiotics in the ICU.

Conclusion: The incidence of VAP is high. Patients of aneurysmal SAH are at higher risk and VAP is as common in patients with supratentorial lesions as in those with infratentorial pathologies. The increase in resistance to the commonly used antibiotics is a cause for concern. Efforts should be taken to evolve more effective preventive measures.

Key Words:

Aneurysmal subarachnoid hemorrhage, Glasgow coma scale, supratentorial etiology, ventilator-associated pneumonia

Key Message:

The incidence of ventilator associated pneumonia is high among patients with a Glasgow Coma Scale score of greater than 8, undergoing a neurosurgical procedure, and postoperatively receiving mechanical ventilation for greater than 48 hours. The most commonly affected patients included those poor grade patients suffering from aneurysmal subarachnoid hemorrhage. The increase in resistance to commonly used antibiotics is a cause for concern and immediate steps should be undertaken to address this issue on a national level.

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Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection reported in mechanically ventilated patients in the intensive care units (ICUs). VAP is defined as pneumonia that occurs 48 hours or more after an endotracheal intubation or tracheostomy,

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caused by infectious agents not present or incubating at the time of mechanical ventilation, and is characterized by the presence of a new or progressive infiltrate, signs of systemic infection (increased body temperature or altered blood cell count), changes in sputum characteristics, and detection of the causative agent.[1] VAP prevention has been now recognized as an important patient-safety initiative and a health care quality indicator.[2] It has been estimated that about 200,000 patients per year require mechanical ventilation (MV) secondary to neurological injury[3] and the incidence of VAP is reported to be 40–50% in this population.[4] VAP requires an early diagnosis and initiation of appropriate antibiotic treatment, as any delay in the administration of appropriate antibiotic therapy results in an increased hospital mortality, as reflected in other studies.[5] The rate of risk of developing VAP is reflected more accurately by calculating the incidence rates using 1,000 ventilator days as the denominator. VAP rates have ranged from 4–14/1000 ventilator days in the United States and 10–52.7/1000 days in the developing countries.[6] The early onset of pulmonary infection and the peculiar microbial pattern in the neurological patients relates to oropharyngeal or gastric colonization, followed by a high volume aspiration of oropharyngeal secretions shortly after brain injury, during resuscitation, and as a consequence of intubation.[4] Neurosurgical risk factors that also contribute to the development of early VAP include the use of barbiturates, continuous sedation, intracranial hypertension, and delayed enteral feeding.[7] Some studies have reported the high association of VAP in paitents who have suffered from a subarachnoid hemorrhage (SAH).[7] A higher incidence of VAP has also been reported in patients with a Glasgow coma scale (GCS) score<9, and in patients with traumatic head injury, as compared to the rest of ICU patients.[8]

The purpose of our study was to determine the incidence of VAP in the neurosurgical ICU patients and also to assess the probable contributing neurosurgical risk factors in the development of VAP, like the site and nature of lesion in brain, duration of surgery, blood loss during surgery, and infection elsewhere in the body.

Materials and Methods

After obtaining clearance from the institutional ethical committee, a prospective observational clinical study from February 2015, which included patients with GCS >8 undergoing a neurosurgical procedure and postoperatively receiving MV for >48 hours, of the age group of more than 1 year, were followed up for the development of VAP. A detailed history including the age, gender, underlying neurosurgical clinical condition, any history of previous antibiotic intake, date of intubation and extubation, total number of days of MV, treatment being administered in the ICU and the assessment of probable neurosurgical risk factors contributing to VAP were analyzed. The diagnosis of VAP was based on clinical (fever, altered white blood cell count) and microbiological criteria, according to the Centers for Disease Control (CDC) guidelines. The diagnosis was confirmed when positive quantitative culture was obtained in the endotracheal tube (ET) aspirate samples (i.e., non-bronchoscopically obtained bronchoalveolar lavage [BAL] specimen). VAP rate was defined as the 'Number of VAP cases × 1000/Total ventilator days'.[6]

Technique for sampling

Endotracheal aspirate (ETA) samples were collected from all postoperative neurosurgical ICU patients who received MV for more than 48 hours.[9] Patients who were already intubated before admission to the ICU or who died within 48 hours were excluded. Blind endotracheal aspiration was performed with a sterile catheter technique using a 10–12F suction catheter with a mucus trap. The catheter was introduced till resistance was felt (at the level of the carina), and then the catheter was withdrawn about 1 cm, followed by tracheal secretion aspiration. A minimum of 2 ml of endotracheal aspirate was collected from each patient on the 2nd, 4th, and 7th day and on subsequent days, depending upon the clinical scenario. All the samples were immediately transported to the laboratory.

All samples were processed in the microbiology laboratory by semi-quantitative culture and colony counts, as per the CDC guidelines. Bacterial identification and antibiotic susceptibility tests using standard methods were performed for samples showing a positive growth ($\geq 10^4$ colony forming units), as defined by the CDC guidelines.[10]

Statistical analysis

All VAP positive patients were analyzed to determine the risk factors present in them. Descriptive data was expressed in numbers and percentages. Student's *t* test and chi-square test was used to analyze the comparison of categorical variables. IBM SPSS Statistics 19.0 (Statistical Package for the Social Sciences) was used to analyze the data. A *P* value <0.05 was taken as significant.

Results

A prospective clinical study was conducted in our institution from February 2015 to November 2015. A total of 596 patients were evaluated, of which 71 patients, who were on MV for more than 48 hours were included in our study. Among them, 49 (70%) patients fulfilled the clinical and microbiological criteria for the confirmation of VAP. The incidence of VAP in our study was 70%. The VAP rate calculated in our study was 25.11 per 1000 ventilator days, as the total number of VAP cases were 49, and total ventilator days for 71 patients ventilated for more than 48 hours were 1951.

Among the 71 patients, 38 were male, of whom 26 (68.42%) patients developed VAP. Of the 33 female patients, 23 (69.70%) developed VAP. The difference was found to be statistically insignificant. Among the 49 patients who developed VAP, there were more males (54%) than females (46%) and in different age groups, the incidence of VAP was highest in patients who were of more than 50 years of age (33%).

Out of the 49 cases, 15 patients (31%) were categorized under the early onset group (<5 days) and 34 (69%) under the late onset group (>5 days). *Acinetobacter baumannii* was the most common organism found in the early onset VAP, and *Pseudomonas aeruginosa* was the most common organism found in the late onset VAP.

While analyzing the development of VAP in relation to the underlying neurosurgical condition, a subgroup analysis revealed that VAP was more common in

patients with aneurysmal SAH, modified Hunt and Hess grade 3–5 (14/49; 29%). None of the cases with SAH grade 1–2 had VAP in our series. Posterior fossa surgeries were found to have a higher incidence (9/49; 18.36%) of VAP as compared to meningiomas (8/49–16.32%) and craniovertebral junction and cervical spine surgery (10.20%), as shown in Table 1. The trends were clinically important and yet had no statistical significance. (odds ratio [OR]: 1.066, 95% confidence intervals [CI]: 0.346–3.284, *P* value 0.091).

With regard to the site, among a total of 71 patients, there were 39 patients with an etiology related to the supratentorial compartment and 32 paitents with an etiology related to the infratentorial compartment. In VAP-positive patients, the supratentorial compartment etiologies (26/49; 53.06%) had a higher incidence as compared to the infratentorial compartment etiologies (18/49; 36.73%) and those at the craniovertebral junction and the cervical spine (5/49–10.21%) [Table 2]. This observation again was found to be clinically significant but statistically insignificant (χ^2: 0.040, $P = 0.839$).

Regarding the duration of surgery, the patients did not show any significant difference in the development of VAP. However, in our series, patients who underwent a prolonged surgery and required elective postoperative ventilation were extubated within 48 hours in the majority of cases and did not qualify for being included in this study on VAP.

An association was also noted in relation with infection elsewhere in the body. A concurrent infection was often seen with seven patients having an urinary tract infection, five patients having a blood stream infection, and four patients having a surgical site infection. The incidence of VAP increased in patients who were on MV for >15 days (80%) as compared to those who were ventilated for ≤15 days (20%) [$P < 0.01$].

In our study, among the 71 patients, there were 9 patients who had a significant intraoperative blood loss (>30% of total blood volume) that resulted in hemodynamic instability; among these patients, 6 (66.67%) patients developed VAP in the postoperative period. Among 62 patients, who had a blood loss <30% of total blood volume, 43 patients (69.35%) developed VAP. However, there was no statistical significance in both the groups (χ^2: 2.24, $P = 0.138$).

The incidence of pulmonary complications was significantly more in patients who received blood transfusion during the intraoperative period. In our series, a higher incidence of VAP was noted in 20/49 (41%) patients who received an intraoperative blood transfusion as compared to 5/22 (22.72%) who did not, and the difference in the development of VAP in the two groups of patients (those who required a blood transfusion and those who did not) was found to be statistically significant ($P < 0.05$).

Out of the 49 patients who had VAP, 33 (67%) underwent a tracheostomy. Nineteen patients underwent an early (≤10 days), and 14 patients, a late (>10 days) tracheostomy. It was seen that patients with an early tracheostomy had lesser duration of MV and an early weaning from the ventilator, and hence, a shorter duration of ICU stay as compared to patients who underwent a late tracheostomy. Patients who underwent an early tracheostomy had a mean duration of MV, ICU stay, and hospital stay of 23.93 ± 11.49, 28.96 ± 14.44, 37.34 ± 17.33 days, respectively, as compared to 35.82 ± 7.35, 39.60 ± 7.65, 47.62 ± 7.59 days, respectively, in patients who underwent a late tracheostomy, with a highly significant *P* value for all the three variables ($P < 0.001$).

In our study, among the 71 patients, there were 12 patients on broad spectrum antibiotics in the preceding 5–7 days, of whom 9 patients (75%) developed VAP in the postoperative period. Of the 59 patients, who were not on antibiotics in the preceding 5–7 days, 40 patients (67.80%) developed VAP. However, there was no statistical significance in both the groups ($P > 0.05$).

In the majority of patients who developed VAP, 96% of bacterial isolates were found to be gram-negative bacilli. *Acinetobacter baumannii* accounted for 32% of cases of VAP followed by *Pseudomonas aeruginos*a (which was responsible for 26.66% of cases of VAP), and *Klebsiella pneumoniae* (24%). Other gram-negative bacilli isolated were *Citrobacter freundii*, the *Enterobacteriaceae* species, *Escherichia coli*, and *Proteus mirabilis* [Table 3]. Out of the total of 75 isolates, only 3 isolates were those of gram-positive bacteria, of which 2 were *Staphylococcus aureus* and 1 was Enterococcus spp. Among the total 49 cases of VAP, 31 cases had polymicrobial and 18 had monomicrobial organisms. In the monomicrobial cases, gram-negative isolates accounted for 95% of the cases; and, even in the polymicrobial cases of VAP, gram-negative isolates were predominant.

Another alarming observation was the higher resistance rates among the commonly used antibiotics in the ICU. This included

Table 1: VAP in relation to the underlying neurosurgical condition

Nature of Lesion	Total	VAP patients *n* (%)	Non-VAP patients (*n*)	Percentage of VAP patients (out of 49 patients)
Aneurysmal SAH (Grades 3, 4, 5)	18	14	4	28.56%
Posterior fossa (including CP angle)	12	9	3	18.36%
Meningioma	11	8	3	16.32%
CV junction and cervical spine	7	5	2	10.20%
High-grade glioma	7	5	2	10.20%
Intraventricular lesion	3	2	1	4.08%
Clival chordoma	2	1	1	2.04%
Sellar suprasellar mass	2	1	1	2.04%
Miscellaneous	9	4	5	8.16%
Total	71	49	22	100%

VAP = Ventilator associated pneumonia; SAH = Subarachnoid hemorrhage; CP = Cerebellopontine; CV = Craniovertebral; *n* = Number

resistance to medicines like penicillin, third generation cephalosporins, quinolones, tetracyclines, and vancomycin. The least resistance was seen to colistin (90–95% sensitive), tigecycline (85–90% sensitive), imipenem (80% sensitive), and piperacillin-tazobactam (50%) [Table 4]. All gram-positive organisms were sensitive to linezolid and newer generation antibiotics like teicoplanin.

The overall mortality associated with VAP was observed to be 36/49 (74.17%). It was highest in patients in the age group of >45 years (13/36; 36.11%) [$P > 0.05$].

Discussion

The overall incidence of VAP in our study was 70%. This figure is at the higher end of the range of 15–58% reported by other investigators.[11] The higher incidence of VAP in our study may be attributed to several factors such as the heterogeneity existing in the study population, the differences in the definition of VAP (e.g., whether the clinical or microbiological criteria or both were chosen), and possibly, due to the differing magnitude of the preventive strategies used in different intensive care unit settings. Our study included elective post-operative patients who underwent a neurosurgical procedure and were mechanically ventilated for more than 48 hours. In comparison, other studies often also encompassed all patients admitted to the ICU including those who had undergone a severe traumatic brain injury.

Other factors influencing the results included the duration of study and the total number of cases, which were lesser as compared to the other studies that were showing a lower incidence. Additionally, a high incidence of VAP may be due to the lack of adequate nursing staff (nurse to patient ratio should ideally be 1:1 as compared to 1:3 in our institute), which may have adversely affected the quality of care given to the patients. There is increasing evidence to demonstrate that a low staffing level and a higher work load increases the risk of a negative outcome among ICU patients that may be related to healthcare-associated infections and death.[12]

Table 2: VAP in relation to site of lesion

Site of Lesion	Number of VAP patients *n* (%)
Supratentorial	26 (53.04%)
Infratentorial	18 (36.73%)
CV junction and cervical spine	5 (10.21%)
Total	49

VAP = Ventilator associated pneumonia; CV = Craniovertebral; *n* = Number

Table 3: Microbiological profile of VAP patients

Microorganisms	Number of bacteria isolated
Acinetobacter baumannii	24 (32%)
Pseudomonas aeruginosa	20 (26.66%)
Klebsiella	18 (24%)
Other Gram-negative organisms	10 (13.33%)
Gram-positive organism	3 (4%)
Staphylococcus aureus	2
Enterococcus aureus	1
Total	75

Table 4: Antibiotic sensitivity pattern in Gram-negative organisms

Antibiotic	Percentage
Polymyxin Colistin	90-95
Tigecycline	85-90
Imipenem (Carbapenems)	80
Piperacillin Tazobactam	50

On analysis of the association of VAP with various etiologies, we observed that aneurysmal SAH (grade 3, 4, 5) was the most common underlying condition (29%) followed by posterior fossa surgery, meningiomas, and pathologies of the craniovertebral junction and the cervical psine. These findings are rather unique.

The exact mechanism of the increased incidence of VAP in patients who present in a poor grade after having suffered from a SAH is not properly understood. Immunosuppression has been found to be associated with a higher incidence of pneumonia in symptomatic aneurysmal SAH patients. Sarrafzadeh *et al.*,[13] documented the persistent suppression of the cellular immune response and an impaired proinflammatory cytokine release by monocytes and lymphocytes in symptomatic aneurysmal SAH patients (World Federation of Neurosurgical Societies [WFNS] grades 3–5); whereas in asymptomatic patients (in low WFNS grades 1–2), the parameters indicated the immunocompetence of the patient who recovered within 3 to 5 days after the occurrence of aneurysmal SAH. Pneumonia (67%; $P = 0.011$) was reported to be more frequent in symptomatic patients with a SAH and was attributed to immunodepression.

Another proposed "catecholamine hypothesis" explaining the higher incidence of VAP in SAH is related to the trigger of a massive sympathetic nervous system activation. This may lead to a sudden and sustained increase in the circulating cerebrospinal fluid and urine catecholamines that may be associated with the production of toxic cytokines and end-organ catecholamine-mediated injury, including a high pressure pulmonary edema and aspiration pneumonia.[14]

The surge in intracranial pressure (ICP) and activation of the sympathetic nervous system contributes to SAH-induced systemic inflammatory response syndrome (SIRS). Patients undergoing aneurysm surgery have an increased likelihood of developing SIRS with the reported incidence ranging from 29% to 87% in patients with SAH. SIRS often contributes to the acute lung injury and a poor outcome after SAH.[15,16]

The use of neuroprotective measures like hypothermia and barbiturate administration in combating raised ICP may result in immune suppression, decreased leukocyte counts, and may, in all likelihood, predispose to pneumonia.[17] Diminished level of consciousness, use of sedatives and an impaired cough reflex may result in aspiration pneumonitis and basal atelectasis.

Additionally, vasospasm after SAH may result in ischemic neuro-degeneration of the dorsal root ganglia of the phrenic nerve and in phrenic nerve root ischemia. This mechanism is suggested to play an important role in the deterioration of respiratory rhythm following experimental SAH.[18] Furthermore, the overload of blood volume can be another

contributing factor to the development of pulmonary edema. Administration of blood may be the first intervention performed to maintain the cerebral perfusion pressure and to reduce the effects of vasospasm due to aneurysmal SAH.

Regarding the site, contrary to the prevalent belief of the patients with an infratentorial compartment lesion having a higher incidence of VAP, our study found that patients with a supratentorial compartment pathology had a higher incidence (53%) of VAP.

Intraoperative blood loss and the subsequent blood transfusion had an impact on the postoperative pulmonary complications. Significant intraoperative blood loss leads to hemodynamic instability and relative ischemia causing ischemic-reperfusion injury, which results in major organ dysfunction. Blood transfusion causes immunosuppression and immunotolerance, which in turn predisposes to nosocomial and postoperative infections. Immunomodulation related to blood transfusion also correlated with an increased rate of pulmonary complications.[19]

Another unique finding in our study was the duration of mechanical ventilation and its association with VAP. It was observed that the incidence of VAP increased with the duration of MV. Thus, VAP was seen in 80% of the patients who were ventilated for >15 days as compared to 20% among those who were ventilated for less than ≤15 days [$P < 0.01$]. These findings were similar to an Italian study that included 724 ICU patients, in which the incidence of VAP increased from 5% for patients receiving MV for 1 day to 69% receiving ventilation for ≥30 days.[20]

Administration of broad spectrum antibiotics in the preceding 5–7 days also contributes to the VAP rates. It was observed that out of the 49 patients who developed VAP, 9 (18.37%) were on broad spectrum antibiotics in the preceding 5–7 days. Furthermore, prolonged antibiotic administration to ICU patients for the treatment of primary infection results in a "super infection", from the selection of and the subsequent colonization of resistant pathogens. A seminal study in a French ICU noted that the rate of VAP caused by *P. aeruginosa* and *Acinetobacter* spp. markedly increased in patients who were on a prior antimicrobial therapy. These two pathogens were responsible for 65% of VAP cases in patients who had previously received antibiotics as compared to only 19% of VAP cases among those who had not received any prior antibiotics.[21] In our study also, these two pathogens accounted for 60% VAP cases; Acinetobacter spp. accounted for the highest number of cases followed by *P. aeruginosa*. Joseph *et al*., also reported *Acinetobacter* spp. and *P. aeruginosa* as the predominant organisms causing VAP.[22] In another study by Gupta *et al*., the most common pathogen was *P. aeruginosa*.[23]

Airway intubation predisposes the upper and lower respiratory tract to an increased colonization by the gram-negative bacteria resulting in their subsequent overgrowth and the development of pneumonia. Non-fermenters such as *Pseudomonas* spp. and *Acinetobacter* spp. were significantly associated with late onset VAP, as observed in other studies, but in our study, *Acinetobacter* was the most common organism, even in patients with early onset VAP. In their study, Giantsou *et al*., also noticed that in both the early onset and late onset VAP, multi-resistant *P. aeruginosa* was the most common organism isolated.[24]

Regarding the antibiotic sensitivity pattern, our results were in accordance with the study conducted by Dhadke *et al*., in which gram-negative organisms were resistant to the commonly used antibiotics and showed sensitivity to the colistin or the imipenem group. Similarly, gram-positive organisms showed a sensitivity to linezolid.[25]

In the present study, the endotracheal aspirate samples from the mucus trap were taken from each patient. Wu *et al*., have shown that quantitative cultures using invasive bronchoscopic methods were comparable to those taken by endotracheal aspirates.[26] VAP has been associated with a mortality rate between 24–76%, observed at different institutions. Patients with VAP are estimated to have a 2–10 fold higher rate of mortality as compared to the ventilated patients without pneumonia.[27] The overall mortality in patients with VAP in our study was 74.17%. This figure was comparable to that of the study done by Mukhopadhyay *et al*., in which the overall mortality rate among patients with VAP was 67.3%.[28]

Conclusions

VAP is a big challenge in the setting of neurosurgical ICU. This study highlights the neurosurgical risk factors associated with VAP so that adequate preventive measures can be implemented. VAP occurs more in patients with subarachnoid hemorrhage than in patients suffering from other etiologies and is as commonly assocated with the supratentorial lesions as the infratentorial ones. A higher incidence of VAP is also noted in patients who required blood transfusions and in those who underwent a late tracheostomy. Understanding the microbiological milieu of the neurosurgical ICUs and their resistance pattern could aid in the prompt diagnosis of VAP and aid the institution of an early and effective treatment of the affected patients.

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Conflicts of interest
There are no conflicts of interest.

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