Pakistan Journal of Neurological Sciences (PJNS)

Volume 15 | Issue 1 Article 11

3-2020

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Usman Siddiqui
Aga Khan University, Karachi

Muhammad Faheem Khan
Aga Khan University, Karachi

Saad Bin Anis
Aga Khan University, Karachi

Bushra Ahmad
Aga Khan University

Muhammad Shahzad Shamim
Aga Khan University, Karachi

See next page for additional authors

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Authors
Usman Siddiqui, Muhammad Faheem Khan, Saad Bin Anis, Bushra Ahmad, Muhammad Shahzad Shamim, Rida Mitha, Fouzia Anis Khan, and Erfan Hussain

FACTORS PREDICTING NEED FOR POST-OPERATIVE VENTILATION AFTER MICROSURGICAL CLIPPING OF CEREBRAL ANEURYSMS – A MULTIVARIATE ANALYSIS

Usman Siddiqui[1], Muhammad Faheem Khan[1], Saad Bin Anis[1], Bushra Ahmad[1], Muhammad Shahzad Shamim[1], Rida Mitha[1], Fouzia Anis Khan[1], Erfan Hussain[1]
[1]. Aga Khan University Hospital, Pakistan.

Correspondence to: *Saad Bin Anis E-mail: saad.anis@aku.edu*

Date of submission: *August 26, 2019* ***Date of revision:*** *January 05,2020* ***Date of acceptance:*** *January 11,2020*

ABSTRACT:

INTRODUCTION:
Patients with aneurysmal Subarachnoid Hemorrhage (aSAH) frequently require Intensive Care Unit (ICU) beds, pre-operatively and more often, post-operatively due to the need for ventilatory support and specialized monitoring. We aimed to evaluate the frequency of post-operative ventilatory requirement in patients with aSAH and identify the possible predictive factors that might influence the need of post-operative ventilation in these patients.

METHODS: We retrospectively identified a five-year data of all patients with aSAH who underwent surgical clipping using a structured proforma. Aneurysm was confirmed by Digital Subtraction Angiography (DSA) or Computerized Tomographic Angiography (CTA).

RESULTS: Seventy-eight patients were identified during the defined period. Ventilators and ICU beds were asked to be reserved for 66 (84.6%) patients pre-operatively. Of these only 24 (36.4%) patients failed to be successfully extubated and therefore required ventilatory support. On univariate regression analysis clinico-radiological factors such as WFNS grade ≥ 4 (p-value: <0.001), Hunt and Hess grade ≥ 4 (p-value: <0.001), Fischer grade of ≥ 3 (p-value: 0.002), Glasgow Coma Score (GCS) score of ≤ 12 (p-value: <0.001), External Ventricular Drain (EVD) insertion, an intra-operative blood loss of > 500ml and emergency surgery (p-value: 0.001, 0.004 and 0.031 respectively) were all independently associated with a higher chance of failure to extubate. On multivariate logistic regression analysis GCS score of ≤ 12 (p-value: 0.001) fared critical for extubation failure adjusting for the blood loss of ≥ 500ml (p-value: 0.061).

CONCLUSION: The demand for post-operative ICU and ventilatory support is over estimated than the actual need. Although multiple clinico-radiological factors can individually predict the need for post-operative ventilation, however GCS score of ≤ 12 remains crucial in the final decision making seen in our small cohort of patients.

KEY WORDS: Cerebral Aneurysm, Craniotomy, Clipping, Subarachnoid Hemorrhage, Ventilation.

ACKNOWLEDGEMENTS: The authors would like to thank Dr. Khabir Ahmed, Department of Surgery, Aga Khan University for his help in the analysis.

Abbreviations
aSAH: Aneurysmal Subarachnoid Haemorrhage SAH: Subarachnoid Haemorrhage CNS: Central Nervous System
ICU: Intensive Care Unit SCU: Special Care Unit CTA: Computerized Tomographic Angiography
DSA: Digital Subtraction Angiography GCS: Glasgow Coma Score TCD: Transcranial Doppler CVP: Central Venous Pressure OR: Operating Room HHT: Hypertensive Hypervolemic Therapy MAP: Mean Arterial Pressure ICP: Intracranial Pressure IVH: Intra Ventricular Haemorrhage ICH: Intracranial Hypertension EVD: External Ventricular Drain
MCA: Middle Cerebral Artery ACA: Anterior Cerebral Artery ICA: Internal Cerebral Artery Pcom: Posterior Communicating Artery Acom: Anterior Communicating Artery CSF: Cerebro-Spinal Fluid DRC: Departmental Review Committee, Aga Khan University ERC: Ethical Review Committee, Aga Khan University ICD-9: International Classification of Diseases – version 9

INTRODUCTION: The numbers of specialized ICUs are limited in most developing countries.[1, 2, 3] Hospitals in these countries rely on a central ICU that caters to all surgical and medical sub-specialties.[4] Patients with aSAH are admitted to ICU and are cared for by a multidisciplinary team including intensivists and neurosurgeons. An ICU bed is even more important if the patient is undergoing craniotomy and microsurgical clipping of aneurysm, and typically an ICU bed with standby ventilator is reserved for post-operative care in case the need arises. This may potentially lead to a few problems. For one, the unavailability of bed in the ICU leads to a delay in surgery and definitive care for these patients. Secondly, reserving beds for the duration of surgery prevents any subsequent patient in need to avail the ICU bed. Through this study, our aim was to evaluate the frequency of post-operative ventilatory requirement and to identify predictive factors that might influence the need of post-operative ventilation in similar patients.

METHODS

The study was conducted at the Aga Khan University Hospital, Karachi. Our center has three distinct levels of care; the general ward, an intermediate level Special Care Unit (SCU) further subdivided for surgery and medicine, and the ICU, also subdivided for surgery and medicine, catering to all sorts of adult patients, excluding cardiac, pediatric and neonatal patients, who have separate units. General wards provide routine in-patient care. The SCU is equipped for invasive hemodynamic monitoring and provides a 2: 1 patient to specialized nursing staff ratio but does not accommodate invasive ventilation; a portable ventilator is however available for emergencies to transfer a deteriorating patient to the ICU. The ICU provides 1:1 care, and each bed is equipped with equipment for invasive hemodynamic monitoring, and a ventilator. Intracranial monitoring at the time of preparing this manuscript, was occasionally employed through an external ventricular drain, although the institution has now started formal ICP monitoring through intra-parenchymal bolts.

Patient selection: We retrospectively reviewed charts from July 2009 – July 2014 for patients who were admitted to the neurosurgery service at our institution with a diagnosis of aSAH. The study was exempted by the institutional Ethics Review Committee (ERC). The diagnosis of SAH was based on a positive admission CT scan and/or a positive CSF study. Aneurysm was confirmed by Digital Subtraction Angiography (DSA) or Computerized Tomographic Angiography (CTA). Any patient with a negative DSA/CTA but a positive CSF study had a repeat scan within 1-3 weeks. In patients with a negative initial CT scan and CSF study but a high index of suspicion, based on history and neurological examination, a DSA/CTA was done to rule out the possibility of an aneurysm. If positive, these patients were identified as unruptured aneurysm patients due to lack of evidence for SAH on the initial CT scan and CSF study. Treatment for both these groups however remained the same and is described below. CSF studies are not routinely carried out at our institution for all patients with the diagnosis of SAH. All patients with SAH due to trauma, arteriovenous malformation and an absence of aneurysm on confirmatory tests were excluded from the analysis. Patients with missing record; those who were intubated at presentation due to low GCS < 8; and those who underwent endovascular coiling as a primary procedure were also excluded. A structured proforma was developed for data collection and information pertinent to - demographics, comorbid conditions (diabetes, hypertension, ischemic heart disease, renal dysfunction and chronic pulmonary disease), clinical presentation (GCS), clinical and radiological severity of illness (WFNS grade, Hunt and Hess grade and Fischer grade), size and location of the aneurysm, duration from post-ictus day to surgery, ventilator requested, delay in surgery due to non-availability of ventilator, preoperative external ventricular drain placement, intraoperative blood loss, intraoperative hypotension, duration of surgery, time of surgery with respect to day or night and mode of surgery (emergency surgery versus elective) was carefully tabulated and analyzed.

A total of 112 patients were diagnosed with aSAH. Out of these, 4 patients refused treatment and left against medical advice, 12 patients had either missing relevant clinical information or radiology e.g. those patients referred with outside scans, and 18 patients crossed over for endovascular coiling and therefore were excluded from the analysis.

Clinical Management at our Hospital: Unless a patient with aSAH requires immediate airway control and/or ventilatory support, all patients diagnosed with aSAH were admitted to the SCU. Patients who have GCS of 8 or less are intubated in the emergency room and ventilated therein until a definite ICU bed is available. General measures to reduce, raised Intracranial Pressure (ICP), such as elevating head side to 30-45 degrees, nursing in neutral head position, keeping low level of external stimulation are enforced along with strict input and output charting, neurological examinations every 2 hour and knee high TED hose. Depending upon the clinical condition, the aneurysm is secured as soon as feasible. Typically, patients presenting within three days of aSAH and not suitable for coiling, undergo immediate craniotomy and microsurgical clipping of aneurysm. For the rest, surgery is delayed until vasospasm settles down and clinical condition improves. External ventricular drainage is placed in the Operating Room (OR) in patients with symptomatic hydrocephalus or Intra Ventricular Hemorrhage (IVH) with a diminished level of consciousness. Normal saline (0.9%) is given at a rate of 1.5-2 ml/kg/hour to maintain central venous pressure (CVP) of greater than 8-10 mm Hg and all patients are given oral nimodipine in standard doses, to counter vasospasm. CVP lines are not routinely placed for monitoring volume status in clinically stable patients with a GCS >10; instead vigilant fluid balance is maintained. All patients receive anticonvulsant prophylaxis, proton pump inhibitor, anti-emetics and stool softeners. All non-intubated patients receive oxygen supplementation of 5L by face mask. Vasopressors are given to patients to maintain systolic blood pressure in the high normal range (120 to 150 mmHg). Transcranial Doppler (TCD) flow is performed to rule out or diagnose vasospasm where applicable. Clinical deterioration from delayed cerebral ischemia specially after microsurgical clipping is managed with Hypertensive Hypervolemic Therapy (HHT) to sustain a systolic blood pressure over 180 mmHg and/or Mean Arterial Pressure (MAP) values over 100 mmHg, along with maintenance of cardiac index using inotropic agents such as dobutamine. Computerized tomographic scan is performed to evaluate all instances of clinical deterioration. Symptomatic Intracranial Hypertension (ICH) is treated using 20% mannitol (0.25-1.5g/kg) and/or hypertonic saline 3% (0.25-0.5ml/kg infusion or 3-5ml/kg bolus). A single spike of fever greater than 38.0o C (101.8oF) is treated with a dose of acetaminophen. A fever workup with blood, urine, sputum and/or CSF culture is sent in case of persistent fever. Any patient requiring ventilator support is shifted to the ICU if available. At the time of completion of surgery, the following parameters are used by the anesthetist to assess for safe extubation for all patients. A) Cerebral function adequate for patient co-operation or GCS of more than 8 or consciousness equivalent to preoperative state. B) Hemodynamic stability (lack of vasopressor support and mean arterial pressure within 10–15% of baseline). C) Adequate recovery of muscle strength. D) Normal tidal volumes, normocapnia (end-tidal carbon dioxide 30–45 mmHg), minimum pulse oximetry >95% with FIO2 0.5L. E) Intact gag reflex and swallow function (presence of clearly audible cough during suctioning. Any patient not meeting any of these parameters was shifted to ICU for ventilatory support. Failed extubation was defined as failure to be extubated in OR or the need for tracheal re-intubation within 4-6 hours of their recovery room stay.

Statistical analysis: All data was entered via EpiData software version 3.1 and analyzed using Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS Statistics). Mean and standard deviation were calculated for continuous data. Categorical data was assessed using Pearson's Chi-square. Numerical data were assessed using standard t-tests. When expected number of observations in a contingency table were fewer than 5, Fisher's exact-probability method was used. Univariate analysis was done for all factors to compare the outcome and variables. A P-value of less than 0.05 was taken to be significant. Statistically positive results were further subjected to multivariate regression analysis. To determine the inter-observer variability between ventilator request and use, weighted kappa value was calculated. Inter-observer variability was interpreted as poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61– 0.80), and almost perfect (0.81–1.00) agreement based on the respective kappa score. This was done using Stata v11.2 (StataCorp 1985 - 2009).

RESULTS

We identified 78 patients who underwent craniotomy and microsurgical clipping of aneurysm. Majority (62.8%) of the patients were admitted through the emergency room. Ventilators and ICU beds were asked to be reserved for 66 (84.6%) patients pre-operatively. Of these 66 patients, only 24 (36.4%) patients failed to be successfully extubated and required mechanical ventilation, with 42 (63.6%) patients not requiring post-operative ventilation and were successfully extubated. An inter-observer variability based on the Kappa score was -0.194 which signifies poor agreement when ventilator was asked and needed (p-value: 0.05). Of the remaining 12 patients for whom a ventilator was not requested, only 1 (8.3%) patient failed to extubate successfully (p-value: 0.056). We could also appreciate that the requirement for an ICU bed caused a delay in treatment for 21 patients (26.9%) and led to a 28.6% risk to extubation failure. This however was not statistically significant (p-value: 0.689). Table 1-a and 1-b.

Table 1-a. Ventilator utilization.

Variable		Patients who underwent clipping (n)	Patients who failed trial of extubation (n)	Risk of extubation failure %	P value
Ventilator Requested by Anaesthesiologist	yes	66	24	36.4%	0.056
	no	12	1	8.3%	
Delay Due to Non-Availability of Ventilator	yes	21	6	28.6%	0.689
	no	57	19	33.3%	

Table 1-b. Inter-observer variability.

		Value	Asymp. Std. Deviation	Approx T.	Approx Sig.
Measurement of Agreement	Kappa	-0.194	0.075	-1.914	0.056

Considering the relatively low need of postoperative ventilation as compared to the requests for reservation of ICU beds, we divided patient characteristics into distinct categories in order to identify factors, which might predict a need for postoperative ventilation.

Demographics and clinical assessment: Age was categorized into 4 subgroups. It was observed that age more than 60 years had a higher chance (63.6%) of failure to extubate in comparison to age of less than 40 which carried a 24.0% chance. However, these results were not statistically significant (p-value: 0.109). Similarly, gender and presence of a comorbid conditions like diabetes, hypertension or ischemic heart disease did not seem to affect extubation failure (p-value: 0.328 and 0.420 respectively). None of our patients had renal dysfunction or chronic pulmonary disease which may be coincidental. WFNS grade 4 or more (p-value: <0.001), Hunt and Hess grade 4 or more (p-value: <0.001), GCS score of 12 or less (p-value: <0.001) and emergency surgery (p-value: 0.031) were all independently associated with a higher chance of failure to extubate. Table 2, summarizes the various factors identified.

Table 2. Summary of patient demographics and clinical factors.

Variable		Patients who underwent clipping (n)	Patients who failed trial of extubation (n)	Risk of extubation failure %	P value
WFNS Grade	Grade 1-3	66	15	22.7%	<0.001*
	Grade 4-5	12	10	83.3%	
Hunt Hess grade	Grade 1-3	69	17	24.6%	<0.001*
	Grade 4-5	9	8	88.9%	
GCS score	Grade 13-15	64	13	20.3%	<0.001*
	GCS ≤ 12	14	12	85.7%	
Admission type	emergency	49	20	40.8%	0.031*
	elective	29	5	17.2%	
Age Group	<40	25	6	24.0%	0.109
	40-49	20	6	30.0%	
	50-59	22	6	27.3%	
	60 and above	11	7	63.6%	
Gender	Male	40	14	35.0%	0.328
	Female	38	11	28.9%	
Comorbid Group	Yes	48	17	35.4%	0.420
	No	30	8	26.7%	

Radiological findings: In assessment of the radiological factors, aneurysm location or state at presentation (ruptured vs. unruptured) were not identified as statistically significant (p-value: 0.193; 0.193 and 0.401 respectively). However, patients with large aneurysms (size > 10mm) had a 50% probability to have unsuccessful extubation compared to those with small aneurysms (size 10mm or less) in which the probability was 29.3%. Fisher grade of 3 or more was associated with a higher risk of failure to extubate (p-value: 0.002). Table 3.

Table 3. Summary of radiological characteristics.

Variable		Patients who underwent clipping (n)	Patients who failed trial of extubation (n)	Risk of extubation failure %	P value
Aneurysm Group	Posterior circulation	5	1	20.0%	0.193
	Acom/ACA	24	11	45.8%	
	MCA	34	9	26.5%	
	ICA/Pcom	15	4	26.7%	
Presentation	Ruptured	72	24	33.3%	0.401
	Un-ruptured	6	1	16.7%	
Maximum size	Small ≤10mm	68	20	29.4%	0.193
	Large / Giant >10mm	10	5	50.0%	
Fisher grade	Grade 0-2	35	5	14.3%	0.002*
	Grade 3-4	43	20	46.5%	
EVD	yes	12	9	75.0%	0.001*
	no	66	16	24.2%	

Operative data: Presentation as an emergency through the A&E had a higher rate of failure to extubate (40.8%) when compared to an elective admission for aneurysmal clipping (17.2%). This was also observed to be significant (p-value: 0.031). Aneurysmal SAH with severe hydrocephalus requiring External Ventricular Drain (EVD) insertion, and an intraoperative blood loss of more than 500ml was associated with a greater rate of failure to extubate (p-value: 0.001 and 0.004 respectively). Furthermore, factors such as duration of surgery, surgeries conducted with respect to night/day, and time interval between ictus-and-surgery were not determined as statistically significant to effect extubation failure (p-value: 0.743; 0.439 and 0.316 respectively). Table 4.

Table 4. Summary of operative factors.

Variable		Patients who underwent clipping (n)	Patients who failed trial of extubation (n)	Risk of extubation failure %	P value
Post Ictal Day of Surgery	≤3	23	10	43.5%	0.316
	4-10days	33	8	24.2%	
	≥11days	22	7	31.8%	
Time of Day	Morning	33	9	27.3%	0.439
	Night	45	16	35.6%	
Amount of Blood Loss	≤500ml	27	3	11.1%	0.004
	>500ml	51	22	43.1%	
Duration of Surgery	< 4 hours	20	7	35.0%	0.743
	≥ 4 hours	58	18	31.0%	
EVD	yes	12	9	75.0%	0.001
	no	66	16	24.2%	
Type of admission	Emergency	49	20	40.8%	0.031
	Elective	29	5	17.2%	

After univariate analysis, multiple logistic regression analysis was done for all factors that were statistically significant. In the final regression model after multivariate analysis, the strength of association between low GCS and risk of post-operative extubation failure was statistically significant (p-value: 0.001), adjusting for the effect of blood loss of more than 500ml (p-value: 0.061). In other words, patients with GCS score of 12 or less had a 3.67 times higher relative risk of failure to extubate, independent of other variables. Table 5.

Table 5

Multivariate regression analysis				
	Relative Risk	95% Confidence Interval		Significance
		Lower	Upper	
GCS group				
13-15	1			
≤12	3.67	1.67	8.1	0.001
Blood loss				
≤500cc	1			0.061
>500cc	3.19	0.95	10.77	

DISCUSSION

Hospitals with limited resources such as those in developing countries have significantly fewer established ICU units, [1, 2, 3] primarily due to lack of funds.[5] Most of these institutions do not have sub-specialized intensive care units dedicated for neurocritical care.[4] In these settings, acquiring or reserving a place in the ICU for a patient requiring surgical clipping, can at times take days leading to delay in definitive care, risk of re-bleed, morbidity and/or mortality. Alternatively, these patients may need to be transferred to another hospital which carries its own risks in addition to the loss of valuable time. We retrospectively evaluated the need for post-operative ventilation requirement at our hospital for patients undergoing microsurgical clipping of cerebral aneurysms. In our cohort of 78 patients, a ventilator was not available for 26.9% of the patients when requested, which inevitably led to delayed surgery. Although our results did not indicate any statistical difference in failure to extubate in these cases, it is known that a re-bleed can be devastating; [6] according to various studies, the highest risk of re-bleed is deemed at 6 – 72 hours after the initial presentation. [7, 8, 9, 10] We did not compare the Glasgow Outcome Scale (GOS) for these patients that may have showed similar results as reported in literature. The study identified that only about one-third (36.4%) of the patients for whom a ventilator was requested prior to the surgery, actually required it, identifying what could be an "overuse" of the ICU in a subcategory of the aSAH patients. This observation may prove to be of substantial importance especially in a challenging day-to-day competition for ICU beds, where channeling and directing resources may well make a difference between meaningful survival and ailment in many patients. On univariate regression analysis of various aforementioned factors yielded some expected results. This further strengthened our belief and reinforced the existing knowledge present in literature. To exemplify, a poor Hunt and Hess score, WFNS grade, GCS ≤12 at presentation were all independently responsible with a greater failure rate. These factors have been described in literature with respect to neurological and cognitive outcome, both for short or long-term in a subset of patients with aSAH patients.[11, 12] A study conducted by Rosengart et al., about prognostic factors for outcome in patients with aSAH concluded negative implication of increasing age, presence of comorbid condition along with other factors to poorly affect outcome. [13] Our study did not show any statistically significant differences when comparing similar factors such as age groups, gender and prior comorbid conditions. This may be due to our relatively small sample size, difference in the study objectives and outcome parameters. Radiological data identified mixed results. A high Fisher grade was associated with a statistically compelling risk for extubation failure, while aneurysmal size and location (vessel and division into anterior and posterior circulation) did not have any significant effect. Neurological outcome pertinent to the above has been correlated by various articles. [13, 14] It was interesting to observe that the risk of extubation failure was least (20%) for posterior circulation aneurysms and highest (45.8%) for Anterior Communicating (A-com)/Anterior Cerebral Artery (ACA) aneurysms. This finding may be attributed to only five cases in the former group. Middle Cerebral Artery (MCA) aneurysms and Internal Cerebral Artery (ICA)/Posterior Communicating (Pcom) aneurysms accounted for 26.5% and 26.7% risk respectively. In addition, a higher rate of pre-operative ventilator requirement was seen in patients with MCA; however, we did not find this to be statistically significant.

In a subset of patients who developed hydrocephalus, an EVD was placed prior to microsurgical clipping in 12 (15%) patients, in an effort to improve the clinical condition of patient to minimize post-operative morbidity. This was contemplated after thoroughly explaining the small risk of re-rupture associated with it. It was observed, that 9 (75%) of these patients failed to be extubated after definite surgery, suggesting either hydrocephalus, or placement of EVD to be highly predictive of the need for ventilator support post-operatively. Such patients are usually clinically worse or have a lower GCS and have raised Intracranial Pressure (ICP) that corresponds to a higher failure to extubate rate in this population.

Intraoperative factors including the type of irrigation fluid used, [15] the volume of blood lost during surgery, and the duration of surgery, have all been previously suggested to negatively affect outcome in aSAH patients.[16] Although we could not establish any significant association with the time taken to complete surgery, however our findings reemphasized the need to minimize blood loss to less than 500ml as further loss positively correlated with increased risk for extubation failure. According to common perception, surgery during night-hours is considered to be sub-optimal given the rigorous working hours for surgical team which may lead to psychological as well as physical fatigue and more importantly lack of collateral support if need may arise. Our study failed to show a significant difference in this regard. It was interesting to note that a multivariate logistic regression model used to assess the simultaneous influence of clinical, radiological and operative variables on the outcomes highlighted the importance of GCS as a critical factor to influence need for post-operative ventilation in these patients.

CONCLUSION

This is the first study from this region addressing this aspect, in context of surgical clipping of cerebral aneurysms. The requirement of postoperative ventilation is multi-factorial and the demand is significantly higher in a cohort of aSAH patients who were surgically treated. While the study identifies multiple predictive factors that can potentially aid to predict and guide the decision for requesting a post-operative ventilator especially in a developing or challenged setup, it carries drawbacks inherent to a retrospective design. Moreover, the sample size of our cohort is relatively small and a larger multi-institutional study is needed to confirm these findings.

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Conflict of interest: There is no conflict of interest..
Funding disclosure: Nil
Author's contribution:
Muhammad Faheem Khan was primarily involved in writing of protocol, data collection, data entry, data analysis and manuscript writing & design.
Muhammad Shahzad Shamim developed the idea, contributed in writing and review of the protocol, analysis and manuscript.
Fauzia Anis Khan developed the idea, contributed in intra-operative anesthesia management and review of the manuscript.
Usman Tariq Siddiqui was involved in manuscript writing & design.
Saad Bin Anis was involved with manuscript writing, proof reading and submission.
Bushra Ahmad was involved in data collection and data entry.
Erfan Hussain contributed in the intensive care management and review of the manuscript.
Rida Mitha was involved in review of the manuscript.