Title:- Comparing the empirical therapy of meropenem+ vancomycin with ceftazidime + vancomycin for post neurosurgical meningitis: A cost efficacy analysis

Introduction:

Post surgical meningitis remains a huge burden on health care cost and resources of the hospital. The reported incidence of post neurosurgical meningitis is around 3-5% in the Indian scenario.[1] The causes of postoperative neurosurgical meningitis are multifactorial and they extend from preoperative infected wound, penetrating wound, improper sterility of instruments, CSF leakage and inadequate antibiotic cover. Mostly these infections are caused by iatrogenic infections like Acinetobacter, Klebsiella spp and other gram-negative bacteria. The diagnosis mostly was made by clinical pictures like fever, neck rigidity and rising total leucocyte counts. This was followed by CSF cytology and culture studies. The burden of cost on the healthcare system is magnanimous, financial implications include length of hospital stay, extended ICU stay, ventilator days, cost of further CSF diversion procedures, implantable device removal studies and last but not the least the antibiotic burden. Kourbeti et al found that cost of repair of CSF leak or device removal was included as a direct cost and it exceeded 25% of the overall package cost of the surgery.[2] Role of antibiotics become paramount in such cases and it is mostly seen that meropenem and vancomycin are the drugs of choice in such cases. The meropenem is effective for gram negative and anaerobic cover and adding vancomycin also gives the methicillin resistant staphylococcus aureus (MRSA) cover. Another drug that is effective against post neurosurgical meningitis is ceftazidime, it has good CNS penetration as

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well as it is effective against most of the organisms that causes meningitis in our ICU. Hence, the primary objective of this current study will be to compare both these drugs in terms of disease remission, effect on hospital stay and neurological outcome. Also, the cost efficiency analysis shall be done which will help us to compare the economic burden of the different regimen

Research question/ hypothesis: -

- Does the treatment of post neurosurgical meningitis with meropenem versus ceftazidime leads to better neurological outcome.
- Whether early and robust treatment of post neurosurgical meningitis leads to decreased economic burden on healthcare services

Aims and Objectives: -

1. Neurological outcome in post neurosurgical patients treated with meropenem versus ceftazidime
2. To assess the cumulative economic burden of post-surgical meningitis in an Indian tertiary care hospital

Review of literature: -

Since health care associated meningitis is rare and there has been lot of research going on in this area. HCAM creates a lot of burden on the health care system. Mostly the isolated organism is Acinetobacter and Klebsiella species and most of these bugs and multi drug resistant. [3] Many studies have reported around 10-20% mortality of post neurosurgical meningitis with a 50% relapse rate.[4] GBD 2021 Nervous System Disorders Collaborators published a study in Lancet, they showed that neurological disorders had the highest economic burden in accordance to disability adjusted life years (DALYs), 43% of the

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global population. Among these ten conditions like stroke, neonatal encephalopathy, migraine, Alzheimer's disease and other dementias, diabetic neuropathy, meningitis, epilepsy and neurodevelopmental disorders have the highest morbidity. [5] Most of other studies have evaluated the epidemiology, pathogenesis, incidence and causative aetiology, but very rarely have any study evaluating the overall economic burden of postsurgical meningitis in Indian scenario. Therefore, the goal of this study was to provide the overall burden over a longitudinal observation period and economic impact on a national scale. Before studying the prevalence of post-surgical meningitis, one must take into account the conditions that predispose like HIV/AIDS, certain lymphoreticular malignancies, diabetes, iron chelation and corticosteroid therapies can weaken the host immune system. [6] Children less than 5 years has the increased propensity for neonatal encephalopathy, followed by meningitis and neural tube defects.[7]

A study by Charalambous et al, showed that female sex, old age, Acinetobacter spp and time from initial diagnosis have the maximum impact on the cost of health care.[8] Thy et al, stressed on the fact that direct ICU admission can help these patients rather than shifting to ward. They also said that increased hospital days can be curtailed if such patients are immediately shifted to ICU on first suspicion.[9] Similarly another study agrees that more compliant and robust referral system with a good ICU care can lead to a better neurological outcome and reduce hospital stay.[10]

Materials and Methods:

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Written informed consent, from a relative of all patients who will present to neurosurgery ICU, with signs and symptoms of meningitis, will be taken. After obtaining institutional ethical committee approval, 36 patients will be recruited in each arm of the study (n=72). Patients who will be operated in the department of neurosurgery will be recorded, out of this those patients who shall present with signs and symptoms of meningitis will be identified and the CSF will be sent for cytology and culture. After meningitis is documented based on CSF picture and imaging studies. They shall be divided into 2 groups based on empirical antibiotic regimen.

Groups A: - Meropenem + Vancomycin

Group B: - Ceftazidime + Vancomycin

Further decision about the course of therapy will be taken by antibiotic sensitivity reports and discussion with a microbiologist. The course of treatment will follow according to patient response and clinical profile. Decision for reoperation, abscess drainage and CSF diversion procedures will be taken by the consultant neurosurgeon. Radiological imaging may be done to rule out cerebral abscess or cerebrospinal fluid (CSF) leak. Then CSF shall be send for cytology and cultures and empirical antibiotics started.

Randomisation:-

Allocation of the study patients to the study groups was carried out through computerized randomization chart of serial numbers kept in opaque sealed envelope which shall be opened by the ICU nursing in-charge, who will prepare the study drugs. The patient shall be administered standard dosing regimen according to body weight.

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Cost Analysis and Documentation:-

This cost analysis was performed from a hospital perspective, including detailed healthcare consumption of every individual patient. This study uses direct medical costs, without taking into account health insurance reimbursement. First a cost analysis will be performed based on hospital rate chart analysis and a detailed cost data sheet will be prepared which shall include cost of readmission, ICU charges, reoperation charges, cost of CSF diversion procedure, expensive antibiotic use, cost of physiotherapy and dietician and also if any new device is being put like (shunts, Omaya reservoir).

Inclusion Criteria:

- Patients aged more than 18-65 years
- Postoperative Neurosurgical patients admitted in Neuro ICU AIIMS Kalyani.
- Having Meningitis as shown by clinical and CSF cytology

Exclusion Criteria:

- Hypersensitivity to any antibiotic drugs
- Patient having viral or tubercular or fungal meningitis
- Patient is having renal dysfunction

The detailed cost sheet analysis will be prepared in both the groups. The parameters like length of hospital stay, length of ICU stay, ventilator days,

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tracheostomy , incidence of ventilator associated pneumonia and outcome (Glasgow outcome scale) will be assessed.

STASTICAL ANALYSIS: -

The patient characteristics will be summarized by mean±standard deviation (SD) and range for continuous numerical variables or frequency for categorical variables. Daily expenditure and length of stay for patients diagnosed with post-surgical meningitis during the study period, and up to 1-year follow-up times, will be summarized by their mean±SD values. The 95% confidence interval of patient mortality at each follow-up period was calculated to determine the stability of the estimates. A Kaplan–Meier plot was then generated to visualize length of survival. For all results with p value ≤ 0.05 will be considered significant.

Sample Size calculation: -

Considering mean length of hospital stay in group A as (21.3±12.92 days) and in group B (12.8 ±7.50 days) ; keeping the power of the study as 80% and α as 5% (0.05) ; we calculated a sample size of thirty three (25) in each group. Adjusting for 10% attrition rate we will recruit 22 patients in each group (N=44).

NOVELTY:-

This study makes a decent attempt to analyse the economic burden of managing a post-surgical CNS infection in an Indian tertiary care hospital. This study also tries to compare two different drug regimens for management of meningitis in such cases and thus offers light in those areas that need more research like

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identifying such at risk patients and starting the appropriate empirical drug regimen as soon as possible. Also, the study delves on the neurological outcome in patients who have developed post neurosurgical meningitis (both device or non-device related) and its effect on long term morbidity and mortality.

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SL. NO	CR. NO.	DIAGNOSIS	PRIMARY SURGERY	DATE OF SURGERY	CSF STUDY					LENGTH OF HOSPITAL STAY	LENGTH OF ICU STAY	VENTILATOR DAYS	TRACHEOSTOMY (Y/N)	COST OF ANTIBIOTICS	GOS
					TC	DC	S	P	CULTURE						

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Approximate Budget per Patient (PER DAY)

Group A

SL. NO.	PROCEDURE/ TEST	COST PER DAY (Rs.)	INTERVAL
1	ICU CHARGE	300	EACH DAY
2	CEMRI (Including Consumables)	5000 optional	ONCE
3	CSF CULTURE	400	ONCE
4	CRANIOTOMY	4000 optional	ONCE
5	CSF DRAIN SHUNT	250 optional	ONCE
6	EXTRA VENTRICULAR DRAIN	250 optional	ONCE
7	TRACHEOSTOMY	500	ONCE
8	COMPLETE BLOOD COUNT	60	DAY
9	LIVER FUNCTION TEST	250	EACH DAY
10	RENAL FUNCTION TEST	400	EACH DAY
11	PT/INR	60	EACH DAY
12	URINE (RE/ ME)	25	EACH DAY
13	CSF (TC/DC)	100	5th day
14	CSF (SUGAR/ PROTEIN)	45	5th day
15	INJ. MEROPENEM 1GM	2250	8TH HOURLY
16	INJ. VANCOMYCIN 1GM	1600	12TH HOURLY
TOTAL COST PER DAY		15490/-	

Approximate Budget per Patient (PER DAY)

Group B

SL. NO.	PROCEDURE/ TEST	COST PER DAY (Rs.)	INTERVAL
1	ICU CHARGE	300	EACH DAY
2	CEMRI (Including Consumables)	5000 optional	ONCE
3	CSF CULTURE	400	ONCE
4	CRANIOTOMY	4000 optional	ONCE
5	CSF DRAIN SHUNT	250 optional	ONCE
6	EXTRA VENTRICULAR DRAIN	250 optional	ONCE
7	TRACHEOSTOMY	500	ONCE
8	COMPLETE BLOOD COUNT	60	EACH DAY
9	LIVER FUNCTION TEST	250	EACH DAY
10	RENAL FUNCTION TEST	400	EACH DAY
11	PT/INR	60	EACH DAY
12	URINE (RE/ ME)	25	EACH DAY
13	CSF (TC/DC)	100	EACH DAY
14	CSF (SUGAR/ PROTEIN)	45	EACH DAY
15	INJ. CEFTAZIDIME 1GM	300	12TH HOURLY
16	INJ. VANCOMYCIN 1GM	1600	12TH HOURLY
TOTAL COST PER DAY		13540/-	

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