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Gabapentin Induced ADRs and Cost during Pain Management in Conservatively Treated Patients with Traumatic Brain Injury at MSY-MC and Hospital.

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Abstract: *A study of Pain managementin the patients of Traumatic brain injury (TBI)without CNS complications requiring conservative treatment only, was started at hospital in initial 72 hours of observation and then for next eleven days(total14 days) under trauma division. CT scan of brain and clinical status of patients were used, for guiding the dose of gabapentin i.e.100 mg;300 mg ;400 mgthree times a day (8 hourly), for first three days then twice daily for rest of the treatment, purchased from Government "Janaushadhi" medical stores in Meerut district to eliminate bias with respect to cost, GMP certified manufacturers, adhering to principles of good clinical practices(GCP .Adverse drug reactions (ADR) of gabapentin were closely observed inthese randomly selected 32 patientsand were adequately taken care, as apart from sedation(varied from mild to moderate) in intensity, photo phobia were within clinical manageable limits .patients' attendants were asked to comment on Cost of medication immediately at purchase, was reported to be affordable,(the patients' medical bills were 100% reimbursedimmediately by the funds of trust runningthe MSYMC & Hospital)adhering to the principles of free or affordable treatment topeople atteaching hospital under private medical college.*

Keywords: *Pain, CT scan, Traumatic brain injury, Gabapentin, ADR, Janaushadhi, cost, GMP,GCP.*

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I. Introduction

Over 25%of trauma death of world occur in India with road traffic accidents (55.55%) and fall from height(29.2%) as main mechanisms involved in Traumatic Brain Injuries(1).Majority of patients have CONCUSSION-A sudden but short lived loss of mental function that occurs after a blow or injury to head (TBI). Since the number of Neurosurgeon in India is very small i.e. 1360, 492 allied members and 665 trainees, most being confined to super specialty hospitals(2). The ER physician, in majority of cases examines, establishes line of investigations and initial therapy. The acute phase conservative therapy plays a major role in reducing death rate and other complications such as pain, vertigo which may persist for weeks.TBI patients are treated on standard guidelines, to control swelling within the cranium, which is commonly manifested as "Mid-Line Shift"or changes in frontal horn ratio more than 0.3 (normal)(3–5),these are maintained in "Near Normal Ranges"with proper medication (Diuretics). The main neuro pharmacotherapy target includes analgesia, anti-convulsive, convulsion preventive therapy based on continues patient monitoring by means of CT scans, blood analysis and clinical assessment. Pain management in relatively safe in conscious patients .This complaint is of prime concern and is the main cause of their reporting to tertiary Hospitals in upcoming rural Indian teaching medical college hospitals, now imparting quality medical services and taking care of associated ADRs(6)due to administered medicines , to the otherwise underserved regions.

AIM: Monitoring of Adverse Drug Reactions associated with administration of commercially marketed GABAPENTIN (Pre-quantified generic commercially available dose formulations).

Affordability: treatment costs of gabapentin formulations only. Affordability of treatment (minimum costs) of gabapentin using available government (Janaushadhi) generic dose formulations, to gather with generic brand when dose is to be titrated with body weight.

II. Materials And Methods

Patients with Glasgow Comma Score (GCS) above 8, with complaints of pain in head, within 24 hours of TBI and with alleged history of loss of consciousness(LOC),but without ENT bleeds or CSF leakage, who reported to OPD of Mulayam Singh Yadav Medical College and Hospital (MSYMCH).

Duration of selected patient's treatment:

1st April 2018 to 31st May 2018were considered for this study.

Dose selection for ADR study:

Adverse Drug Reactions associated with administrationof commercial marketedGABAPENTIN(7) (Pre-quantified generic commercially available doses formulations of 100 mg, 300mg, 400mg) in pain management due to concussion after TBI.

CT scan evidence criteria:

No mid-line shift or hematomas as an evidence for conservative management in non-contrast CT SCANS)(8).

Pain reduction Criteria:

Clinical global impression scores for intensity of acute pain assessment.(9,10)

Affordability of treatment has been calculated, using minimum cost gabapentin generic tablet available at government (Janaushadhi) pharmacy. Generics (tablet)alone/combined with most cost effective brand, when doses is to be titrated with body weight were not available, as such formulations are not marketed, was administered. All other expenses and treatment costs have been excluded in this part of study.

Affordability=total cost for 15 days/minimum wage(VDA) of unskilled laborer in district Meerut as INR 6325 per month(11)

All permissions from the ethical committee of institute and patients, patient's relatives were duly obtained. CT scans of all 32 patients have been maintained as records of evidence since then. As per standard protocols the permissions for CT scans(Non-contrast) are with the department of radiology/ in the files of treated patient with MRD.

Inclusion Criteria:

1) Patients included in the study had the Glasgow Coma Score(GCS) of 09-15.
2) No patient had ear-nose-throat bleeding.
3)No patientCerebro-spinal fluid(CSF) leakage.(9)

Adverse drug reactions with respect to gabapentin only

1-Dizziness; 2-Vertigo; 3-Muscular weakness/ Fatigue; 4-Sedation; 5-Allergical Reaction; 6-Causing disability; 7-Prolonged hospital stay; 8-Raised LFT-KFT; 9-Miscellaneous.

Table No. 1: Criteria of treatment

Time Duration Of Studied Cases, Therapy And Date	01 April 2018- 31 May 2018, Last dose of last patient on 10 June 2018.
Number of cases(N)	32 (Thirty Two)
Gender	Males– 16 Females - 16
TBI severity	Mild TBI/ Concussion
Alleged History of Loss of Consciousness	All 32 Patients
ENT bleeding or CSF Leakage	None
Chronic Intoxications by alcohol, smoking and drugs	None
Non-contrast CT scans	All upon reporting to OPD
Hematomas	None
Major complaint	Pain within Head, Neck stiffness etc. were excluded.
Time of head-ache from injury	All immediately after injury
Loss of Consciousness/prior episodes of TBI	None
Average dose of GABAPENTIN in mg used group wise.	100 mg, 300 mg and 400 mg,100 mg will beadded to group I and group III.to titrate doses.
Frequency of dose	Thrice daily for first three days, twice daily for next five days, reduced to single bed-time dose in next seven days.
Treatment review duration	Fifteen days

III. Results

Table No 2: Adverse drug reactions with respect to gabapentin only

1-Dizziness	All patients reported dizziness.
2-Vertigo	None
3-Muscular weakness/ Fatigue	None
4-Sedation	One patient, in Group 1, till 4th day of treatment only.
5-Allergical Reaction	None
6-Causing disability	None
7-Prolonged hospital stay	None
8-Raised LFT-KFT	None
9-Miscellaneous	None
Gabapentin in form of tablets of100 mg, 300 mg were used, 400mg	Affordability=total cost for 15 days/minimum wage(VDA) of unskilled laborer in district Meerut as INR 6325 per month(11)

Table No. 2: Parameters of dose of Gabapentin administered

Groups (Gr)(age in year)	Male (M) & female (F)	Tablet Gabapentin used in mg PER DOSE per patient in each group	Thrice daily dose schedule ; total daily dose in mg per patient for first three days in mg	Total dose in first three days per patient in mg	daily dose @ BD in next five days per patient	Total dose in next five days per patient @ BD in mg	Single dose at bed time @ next 7day per patient total in mg	15 Daydose IN mg
Gr.I (1-12 years)	(2)&(0)	100 mg	100mg@ TDS=300 mg.	900	100mg@BD =200 mg	1000	700	2600
Gr.II(13-25 years)	(8)&(4)	300 mg	300mg@ TDS=900mg	2700	300 mg@ BD=600 mg	3000	2100	7800
Gr.III(26-50 years)	(5)&11)	400 mg	400mg@ TDS=1200mg	3600	400 mg@BD =800mg	4000	2800	10400
Gr.IV (50 years and above)	(1)&(1)	300 mg	300mg@ TDS=900mg	2700 mg	300 mg @BD= 600 mg	3000 mg	2100	7800 mg
Total groups = 4	(total16 male)&(16 female)							

Table No 3: Cost of Gabapentin

7.	8	Gabapentin used in mg PER DOSE in each patient	Thrice daily dose schedule ; total daily dose in mg per patient	first three days per patient Total dose in	Total daily dose @ BD per patient	Total dose in next five days@ BDper patient	Singlebed timedose@ next 7day total per patient	3 Day cost per patient	15 Day cost per patient;(Total% cost for 15 day medswith respect tominimum wages of laborer in Meerut district)
Gr.I (1-12 years)	(2)&(0)	100 mg	100mg@ TDS=300 mg.	900 mg	100mg@BD =200 mg	1000 mg	700 mg	INR 39.15= 40	INR 91.67 BRAND; (2%)
Gr.II(13-25 years)	(8)&(4)	300 mg	300mg@ TDS=900mg	2700 mg	300 mg@ BD=600 mg	3000 mg	2100 mg	INR 22.23 = 22.50	INR 54.34 JANAUSHADHI(1.2%)
Gr.III(26-50 years)	(5)&(11)	400 mg	400mg@ TDS=1200mg	3600 mg	400 mg@BD =800mg	4000 mg	2800 mg	INR 61.50	INR 146.01 BRAND+ JANAUSHADHI (3.2%)
Gr.IV(50 years and above)	(1)&(1)	300 mg	300mg@ TDS=900mg	2700 mg	300 mg @BD= 600 mg	3000 mg	2100	INR 22.50	INR 54.34 JANAUSHADHI (1.12%)
Total groups = 4	(total16 male)&(16 female)								100 mg was available as brand added to group I and group III.*

*To keep the cost of treatment at minimum price.

Table NO. 4:

CLINICAL GLOBAL IMPRESSION SCORES FOR INTENSITY OF ACUTE PAIN ASSESMENT(9,10)									
Score	interpretation	No of pt	ADR= dizziness	sedation	Loss of coordination	Eye movement	tremors	diplopia	Swelling of limbs
0	No improvement, worsening	01, pt ID 123456	02	02	None	none	none	none	None
1	Mild improvement	01, pt ID 52018389							
2	Moderate improvement	15							
3	Major improvement	15							

Except for one female patient of age grp. 12-25 years who had reported worsening of pain and one minimal improvement in pain all reported moderate to major pain improvement after first three days of thrice daily doses of a specific formulation.

ADRs

In Group I(age 1-12)

→ Single patient reported "sedation" and "inability to face tube light/sunlight"**Duration** from 1st to 2nd day.

→ Single patient reported "vertigo" on taking 1st dose **Duration** of complaint 4 hours only

→ No other ADRs were reported by these patients.

COST OF GABAPENTIN TREATMENT FOR FIFTEEN DAYS:

Varied from1.12 % to 2% with respect to minimum monthly wages of the poorest earner,as determined by U.P. government from October 2017 and are estimated to be valid till 2019 range.(11)

IV. Discussion

The distressed patient report to hospital emergency room with PAIN as a result of TBI in this medical college hospital on outer/rural periphery of district Meerut. The patients with G.C. Score of equal to or less than 8 were promptly shifted to neurosurgical centre for neurosurgical intervention, asCT scans were conductedby hospital's radiology department,confirmed surgically significant abnormalities, Frontal Horn Ratio at the level of head of caudate nucleus(5) more than 0.30 , Persistent coma, unexplained confusion for more than 4 hours, motor response deterioration, focal neurological signs, CSF leakage(3)were also shifted to super specialty hospitals and were managed as per good clinical practices (GCP).

The number needed to treat (NNT) with monotherapy to achieve pain reduction of atleast 50% are 2 to 4(12).Therefore pain reduction efficacy for Gabapentin holds good prospective in this study on local population.

Gabapentin was chosen over pregabalin because of availability in India version (JAN AUSHADHI STORE) because of expiry of twenty years of patent rights since (Pfizer and Park Devis) prescription drug GRALISE 3 patents most importantly 7438927 patent expires on 26 Feb 2024.(13) Also generic 300 mg preparation is available at JAN AUSHADHI (government medical stores) as capsules only, all formulations must be made available at government supported stores.

Gabapentin remains the first line treatment drug of preference in neuropathic pain. The generics thus available have reduced the treatment costs and appears to hold good prospective in Indian scenario, generated evidence could serve as guidelines for other developing/ poor income group nations to provide affordable treatment to patients of TBI for pain management .

V. Conclusion

Gabapentin, due to its minimal ADRs and good tolerance, cost effectiveness and easy availability in NCR Delhi, continues to be the mainstream medicine for neuropathic pain treatment in patients of traumatic pain injury with GCS above 8.

Conflict of interest = NONE

NO funds were used to sponsor this observational study, no additional funds were requested.

Institutional ethical committee was duly consulted for cost affordability analysis, adverse drug reaction assessment, as no new ADR or signals were generated during this study reporting to regional centre was carried out via ADR form of CDSCO,and alltreatment protocols were duly followed.

All patients are treated free at MSY MC& Hospital trust,it included the 32 patients observed here. All principles of good clinical practice were followed.

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