Original Article

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# Comparison of Efficacy of Combination Therapy with Chlorpromazine and Olanzapine with Chlorpromazine alone for Treatment of Hiccups in Traumatic Brain Injury Patients- A Randomised Control Trial

Anaesthesia Section

MEERA SRINIVASAN[1], GHANSHYAM YADAV[2], YASHPAL SINGH[3], ANURAG SAHU[4], SARITA KUMARI[5], ANUP SINGH[6]



## ABSTRACT

**Introduction:** Chlorpromazine belongs to the category of typical antipsychotics or neuroleptics, also known as First-Generation Antipsychotics (FGAs). It is found to be effective in hiccup management by its action as dopamine antagonist in the hypothalamus. Olanzapine act as an antagonist at postsynaptic serotonergic receptors which augment phrenic motoneuronal activity and play a role in the generation of hiccups.

**Aim:** To compare the effectiveness of combination therapy (olanzapine plus chlorpromazine) with monotherapy (chlorpromazine) in Traumatic Brain Injury (TBI) patient admitted to trauma Intensive Care Unit (ICU).

**Material and Methods:** This randomised control trial was conducted between November 2020 to October 2021 on patients aged 18-65 years diagnosed with intracranial injury due to trauma. A total of 100 patients (50 in each group) were randomised into group 1 (patients receiving chlorpromazine 25 mg thrice daily for five days) and group 2 (patients receiving chlorpromazine 25 mg thrice daily and olanzapine 5 mg once daily for five days). The primary outcome measure was to compare cessation or reduction in the frequency of hiccups. Various laboratory parameters were investigated and compared between both the groups on day zero and day five. The secondary outcome was side-effects of the drugs.

**Results:** In the present study, the distributions of age and gender were similar in both groups with mean age of patients being 39.16±13.88 years and 43.30±12.51 years in group 1 and 2, respectively. Cessation of hiccups were found in 29 (58%) of the patients in group 2 as compared to 27 (54%) patients in group 1, which was not statistically significant. However, improvement in the status of patients were observed in 18 (36%) in group 2, as compared to 10 (20%) in group 1 (p-value=0.02). No serious adverse events were documented in either groups.

**Conclusion:** A better outcome was observed with combination of chlorpromazine and olanzapine than chlorpromazine alone, in treating hiccups due to TBI. The present trial has established the role of drugs for managing hiccups caused after TBI.

**Keywords:** Antipsychotic drugs, Intensive care, Trauma

## INTRODUCTION

Hiccups are defined as the repeated spasmodic, involuntary, transient diaphragm contractions, followed by a sudden closure of glottis, causing termination of inspiration [1]. Usually each hiccup episode is of 4 to 60 hiccups per minute, showing more prevalence among adult men, children, and those with co-morbid conditions [2]. Traumatic Brain Injury (TBI) is characterised by various neurological problems like vestibular dysfunction, seizures, headaches etc, with a few reports of hiccups too. The reason could be disruption of corticobulbar and supraspinal reflex arcs regulating respiratory function, as well as the modulatory neurotransmitter inputs into these reflex arcs [3]. The treatment of hiccups pharmacological, non pharmacological and nerve block treatments are based on its aetiology. Interestingly, some of the medications employed for treating hiccups, have also been implicated as its cause (like opioids, steroids, antidopaminergics, benzodiazepines) [4]. This can be related to complex origin of hiccups, possibly involving serotonin, opioid, dopamine, calcium channel, and γ-aminobutyric acid (GABA) pathways in the medulla and brainstem [5]. If not persistent, patients can be treated with simple medications. The common drugs used for hiccups management includes chlorpromazine, metoclopramide, phenytoin, carbamazepine, haloperidol, nifedipine, etc [5].

Chlorpromazine is an antipsychotic drug, the only medication approved for hiccups by the US Food and Drug Administration, with a dosage of 25 mg four times a day, increasing to 50 mg four times a day if required [2]. Persistent hiccups are managed with 25 to 50 mg of chlorpromazine orally every six to eight hours. If still hiccups persist after oral treatment of two to three days, then it can be given intramuscularly or intravenously [6]. Olanzapine, a serotonin-dopamine receptor antagonist, is one of the novel atypical antipsychotics [7,8]. Treatment with olanzapine causes relief of psychotic symptoms and hiccups during the period of acute rehabilitation after severe TBI and a maintenance dose of 2.5 mg once daily leads to remission of Intractable Hiccups (IH), secondary to brain injury [3]. There is no accurate estimate of the prevalence of hiccups in TBI patients admitted to intensive care and neither there is enough literature on the same regarding the nature of the disease and it's management. However there are many reports and case series of hiccups in TBI patients [3,4]. Hiccups have been shown to cause hyperventilation and respiratory alkalosis and in intubated and mechanically ventilated patients it acts as a risk factor for ventilator associated pneumonia. Hence, detailed evaluation and treatment of hiccups in TBI patients are important [3].

Apart from a few case series and reports, there is a lack of high-quality data on the effectiveness of pharmacological or even non pharmacological interventions for hiccups in TBI patients [9]. In order to frame the protocol or guidelines for hiccups, there is a need

for randomised controlled trials of both pharmacological treatments and non pharmacological treatments.

Hence, the present study compared the effectiveness of combination therapy (olanzapine plus chlorpromazine) with monotherapy (chlorpromazine) in TBI patient admitted to trauma ICU. The primary outcome measure was reduction in frequency of hiccups. Secondary outcome was side-effects of the drugs.

## MATERIALS AND METHODS

This randomised control trial was conducted on patients diagnosed with intracranial injury by trauma, between November 2020 to October 2021. The study was approved by the Ethical Committee of Institute of Medical Sciences, Banaras Hindu University (No. Dean/2019/EC/1775 dated 09.12.2019) and the trial was registered under CTRI Registration (CTRI/2020/11/028823 dated 03/11/2020). The nature of study was explained to the patients relative and written consent was obtained from the latter.

**Sample size calculation:** Sample size calculation was done by taking $\alpha$=5%, Power (1-$\beta$)=80%, minimum expected difference between the groups 27%. A total of 96 patients were estimated with 48 patients in each group. To make provision for dropouts if any, 50 patients were enrolled in each group.

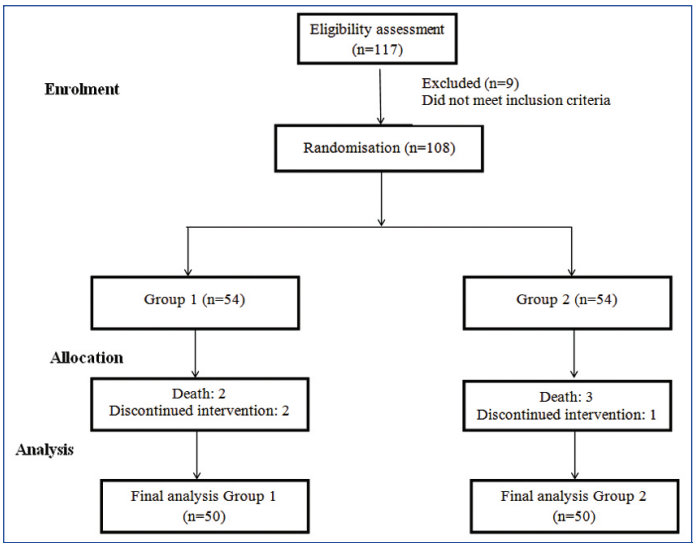
**Inclusion criteria:** All patients of TBI excluding Cerebrovascular Accident (CVA) patients admitted to ICU, age group between 18 to 65 years, with hiccups during study period.

**Exclusion criteria:** Pregnant females, patients with end-organ damage, having diabetes mellitus, hypertension, chronic pulmonary disease, in whom study drug was contraindicated, patients with polytrauma, and those who refused to participate were excluded from the study.

According to the ICU protocol, the patients were managed surgically or non surgically depending upon their treatment requirements. The study drugs were started once the patient started having hiccups. A total of 100 patients (50 in each group) were randomised, based on computer-generated table random number into [Table/Fig-1]:

- Group 1: Patients receiving chlorpromazine 25 mg thrice daily for five days.
- Group 2: Patients receiving chlorpromazine 25 mg thrice daily and Olanzapine 5 mg once daily for five days.

The primary outcome was to compare cessation or reduction in the frequency of hiccups. The Chinese Medicine Medical Association Criteria was used to define cure, cessation or no outcome [10].




**[Table/Fig-1]:** CONSORT flowchart.

All patients were monitored for hiccups and drug related side-effects. Baseline Liver Function Test (LFT), Renal Function Test (RFT), Complete Blood Count (CBC) and Random Blood Sugar Levels (RBS) were recorded before starting the study drug and five days thereafter. The patients, who developed hypotension or sepsis or died during the study period, were considered as dropouts. Patients receiving ondansetron, phenytoin and pantoprazole were also included in the study.

The side-effects of the drugs were recorded based on clinical and laboratory investigations on day zero and day five. Patients were monitored for extrapyramidal symptoms like acute dystonia, seizures, akathisia, Parkinson-like features, allergic symptoms like rash/itching and anticholinergic side-effects like hypotension, urinary retention, constipation, dry mouth. Further, changes in haematological and biochemical parameters were noted. If any patient developed severe adverse event (grade 3 or more, according to the Common Terminology Criteria for Adverse Events), the drug was stopped immediately [11].

## STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 23.0. IBM Corp., NY). Simple descriptive statistics was used (mean±standard deviation) for quantitative variables, and frequency with percentage distribution for categorised variables. For categorical data, Chi-square and Fischer's-exact test was used. For comparing two groups of mean independent Student's t-test was used. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

## RESULTS

A total of 117 patients were assessed for eligibility criteria, out of which nine were excluded, because of not satisfying the inclusion criteria. Therefore, 108 patients were randomised into two study groups (group 1 and 2), out of which eight patients were lost to follow-up (either due to ionotropic support or death), with final value of 50 patients in each group [Table/Fig-1].

The distributions of age and gender in both groups followed normal distribution [Table/Fig-2]. Cessation of hiccups was found in 29 (58%) of patient in group 2 as compared to 27 (54%) patients in group 1. However, reduction in the frequency of hiccups was observed in 18 (36%) of patients in group 2 as compared to 10 (20%) [Table/Fig-3].

| Parameters | Group 1 | Group 2 | p-value |
|---|---|---|---|
| Age Mean±SD (years) | 39.16±13.88 | 43.30±12.51 | 0.121 |
| Gender | Number (%) | Number (%) | |
| Male | 30 (60) | 35 (70) | 0.295 |
| Female | 20 (40) | 15 (30) | |

**[Table/Fig-2]:** Distribution of study subjects according to age (in years) and gender.

| Status | Group 1 | Group 2 | Statistical analysis | |
|---|---|---|---|---|
| | Number (Percentage) | Number (Percentage) | Chi-square | p-value |
| Cessation | 27 (54) | 29 (58) | 1.123 | 1.998 |
| Improvement | 10 (20) | 18 (36) | 2.887 | 0.02* |
| No effect | 13 (26) | 3 (6) | 1.862 | 0.041* |
| Total | 50 | 50 | | |

**[Table/Fig-3]:** Distribution of subjects according to status.
*p-value <0.05 is significant

The intergroup comparison for all laboratory parameters were not significant (p-value >0.05), except platelets, Alanine Transaminase (ALT), serum bilirubin and direct bilirubin which was attributed to selection of patients who have already been on phenytoin for more than 14 days in group 1. At day five however all parameters were non significant [Table/Fig-4,5]. No serious adverse events were documented in either groups.

| Parameters | Group 1 Mean±SD | Group 2 Mean±SD | One sample t-test | |
|---|---|---|---|---|
| | | | t-test | p-value |
| Hb (g/dL) | 10.702.64±2.64 | 10.38±2.74 | 1.740 | 0.088 |
| TLC (cells/cu. mm) | 8260.00±3685.65 | 7940.00±3650.04 | 1.609 | 0.114 |
| Platelet (per litre) | 126400.00±19770.12 | 123400.00±20465.00 | 1.976 | 0.054* |
| Urea (mg/dL) | 29.90±7.03 | 28.70±6.91 | 1.769 | 0.083 |
| Creatinine (mg/dL) | 0.92±0.08 | 0.91±0.08 | 1.941 | 0.058 |
| ALT (U/L) | 55.76±10.04 | 54.40±10.21 | 2.160 | 0.036* |
| AST (U/L) | 56.22±10.30 | 55.18±10.53 | 1.606 | 0.115 |
| ALP (U/L) | 134.20±20.68 | 132.72±20.34 | 1.449 | 0.154 |
| S. Bilirubin (mg/dL) | 0.75±0.20 | 0.73±0.20 | 1.731 | 0.0090* |
| Direct bilirubin (mg/dL) | 0.64±0.12 | 0.61±0.12 | 2.345 | 0.023* |

**[Table/Fig-4]:** Mean values and intergroup comparison between different laboratory investigations in both the groups at Day 0.
Hb: Haemoglobin; TLC: Total leukocyte count: ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; *p-value <0.05 is significant

| Parameters | Group 1 Mean±SD | Group 2 Mean±SD | One sample t-test | |
|---|---|---|---|---|
| | | | t-test | p-value |
| Hb (g/dL) | 10.90±2.53 | 11.18±2.33 | -0.568 | 0.573 |
| TLC (cells/cu.mm) | 8660.00±3777.53 | 8660.00±3777.53 | 0.000 | 1.000 |
| Platelet (per litre) | 129400.00±19315.84 | 125400.00±20524.74 | 1.136 | 0.262 |
| Urea (mg/dL) | 31.1000±6.79811 | 30.20±6.84 | 0.625 | 0.535 |
| Creatinine (mg/dL) | 0.93±0.077 | 0.93±0.07 | 0.531 | 0.598 |
| ALT (U/L) | 58.44±9.58 | 56.78±10.10 | 0.834 | 0.408 |
| AST (U/L) | 58.30±10.63 | 55.92±10.78 | 1.186 | 0.241 |
| ALP (U/L) | 136.94±19.54 | 135.52±19.73 | 0.328 | 0.744 |
| S. Bilirubin (mg/dL) | 0.79±0.20 | 0.78±0.19 | 0.324 | 0.747 |
| Direct bilirubin (mg/dL) | 0.66±0.14 | 0.66±0.14 | 0.000 | 1.000 |

**[Table/Fig-5]:** Mean values and intergroup comparison between different laboratory investigations in both the groups at day 5.

## DISCUSSION

In absence of any effective guideline to treat hiccups in TBI patients, treatment options are limited to use of the various pharmacological drugs. This study aimed to compare the effectiveness of combination therapy with chlorpromazine alone and with combination of olanzapine and chlorpromazine for treatment of hiccups in TBI patients. Although the cessation of hiccup was similar in both groups, improvement in hiccup was statistically significant in group 2 in comparison to group 1 (p-value=0.02). Better outcome in group 2, can be postulated due to a synergistic inhibition of both dopamine and serotonin by chlorpromazine and olanzapine, respectively.

To our knowledge, no similar related studies have been found in literature that compare both drugs for managing hiccups in TBI patients. However, both drugs have shown to be efficacious in managing hiccups in TBI patients [9]. Alderfer BS and Arciniegas DB, showed that in severe TBI, treatment with olanzapine caused relief of psychotic symptoms and Intractable Hiccups (IH) during the period of acute rehabilitation [4]. Another study showed that a maintenance dose of 2.5 mg once daily led to remission of IH secondary to brain injury [12]. In a study by Conley RR et al., olanzapine was compared with chlorpromazine in treatment-resistant schizophrenia and found that olanzapine treated patients show fewer side-effects as compared to chlorpromazine [13].

Chlorpromazine was tested for chronic (obstinate) hiccup, and positive case results were reported by various groups [14-16]. In a study chlorpromazine has shown to cause cessation of hiccups in 82% patients (42/50) in dose of 25-50 mg intravenous, repeated in two-four hours [17]. Another study showed efficacy of 80% (40/50) when used in similar doses [18]. In a study aimed at investigating the clinical efficacy of anisodamine combined with chlorpromazine on intractable hiccups after stroke, the combination therapy showed improvement in 98% patients [19].

Olanzapine is found to act as an antagonist at these postsynaptic receptors, thus attenuating the phrenic excitability, thus relieving hiccups. The most common effect of serotonin on the reflex arcs is in the generation of hiccups at the level of the spinal cord, where serotonergic input augments phrenic motoneuronal activity [4]. Chlorpromazine acts centrally by dopamine antagonism in the hypothalamus and interacts with high affinity to a multitude of receptors and ion channels, thus giving various promising therapeutic effects [4].

Being a low-potency typical antipsychotic, chlorpromazine primarily causes dry mouth, dizziness, urine retention, blurred vision, and constipation by blocking the muscarinic receptors. Despite being a low-potency drug, chlorpromazine can still cause Extrapyramidal Side-effects (EPS) such as acute dystonia, akathisia, parkinsonism, and Tardive Dyskinesia (TD) [4]. Olanzapine is known to cause dyslipidaemia, hyperglycaemia, dry mouth, weight gain, increase in appetite, dystonia and metabolic syndrome [20].

Transient, non dose-dependent, asymptomatic elevations in liver enzymes have also been noted in olanzapine-treated patients [21]. However, no adverse clinical and biochemical events were recorded in the present study and both drugs were well-tolerated. The findings of this study will influence future decisions concerning resources and planning for trials and making guidelines for treating hiccups in ICU for TBI patients.

### Limitation(s)

The study was limited to trauma Intensive Care Unit (ICU) of a tertiary care hospital on a limited sample size. Other drugs frequently used in intensive care setting such as metoclopramide, and ondansetron may interact with the hiccups reflex arc and can precipitate or can cause remission of hiccups [22].

## CONCLUSION(S)

The study revealed that a better outcome was observed with combination of chlorpromazine and olanzapine drugs than chlorpromazine alone. The treatment approach is mainly based on various case series, and observational reports but still clear-cut guidelines are lacking. The treatment of hiccups is mainly based on managing the underlying cause. Drug therapy should be reserved for treatment of hiccups when physical manoeuvres have failed. Still an inadequate data is available to formulate the exact treatment guidelines for persistent hiccups.

## REFERENCES

[1] McFarling DA, Susac JO. Hoquet diabolique: Intractable hiccups as a manifestation of multiple sclerosis. Neurology. 1979;29:797-801. Doi: https://doi.org/10.1212/WNL.29.6.797. PMID:221856.
[2] Marinella MA. Diagnosis and management of hiccups in the patient with advanced cancer. J Support Oncol. 2009;7(4):122-27.
[3] Alderfer BS, Arciniegas DB. Treatment of intractable hiccups with olanzapine following recent severe traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2006;18:551-62. Doi: https://doi.org/10.1176/jnp.2006.18.4.551. PMID: 17135383.
[4] Woelk CJ. Managing hiccups. Can Fam Physician. 2011;57(6):672-75. PMID: 21673211; PMCID: PMC3114667.
[5] Smith HS. Hiccups. In: Walsh TD, Caraceni AT, Fainsinger R, Foley KM, Glare P, Goh C, et al., editors. Palliative medicine. New York, NY: Saunders; 2009. pp. 894-98.
[6] Mann SK, Marwaha R. Chlorpromazine. [Updated 2021 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553079/.

[7] Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: Results of an international collaborative trial. Am J Psychiatry. 1997; 154:457-65. Doi: https://doi.org/10.1176/ajp.154.4.457. PMID: 9090331.
[8] Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. Am J Hosp Palliat Care. 2003;20(2):149-54. Doi: https://doi.org/10.1177/104990910302000214. PMID:12693648.
[9] Steger M, Schneemann M, Fox M. Systemic review: The pathogenesis and pharmacological treatment of hiccups. Aliment Pharmacol Ther. 2015;42:1037-50. Doi: 10.1111/apt.13374. PMID:26307025.
[10] Hongliang X, Xuemei C, Shizhao H, Chaofeng L. Acupuncture and cupping for treatment of hiccup in cases of cerebrovascular accident. J Tradit Chin Med. 2006;26(3):175-56.
[11] Cancer Therapy Evaluation Program Common toxicity criteria, 2002 Rockville, MD National Cancer Institute. Available at: http://ctep.cancer.gov/reporting/index.html. [Accessed 7 October 2009].
[12] Thompson A, Ehret Leal J, Brzezinski W. Olanzapine and baclofen for the treatment of intractable hiccups. Pharmacotherapy. 2014;34(1):e4-8. Doi: https://doi.org/10.1002/phar.1378. PMID:24551889.
[13] Conley RR, Tamminga CA, Bartko JJ, Richardson C, Peszke M, Lingle J, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry. 1998;155(7):914-20. Doi: https://doi.org/10.1176/ajp.155.7.914. PMID:9659857.
[14] Moyer JH, Kent B, Knight RW, Morris G, Dizon M, Rogers S, et al. Clinical studies of an anti-emetic agent, chlorpromazine. Am J Med Sci. 1954;228(2):174-89. Doi: https://doi.org/10.1097/00000441-195408000-00007. PMID:13180510.
[15] Stewart BL, Redeker AG. Emesis and hiccough; Treatment with chlorpromazine. Calif Med. 1954;81:203-05.
[16] Jeon YS, Kearney AM, Baker PG. Management of hiccups in palliative care patients. BMJ Support Palliat Care. 2018;8:01-06.
[17] Friedgood CE, Ripstein CB. Chlorpromazine (thorazine) in the treatment of intractable hiccups. JAMA. 1955;157(4):309-10. Doi: https://doi.org/10.1001/jama.1955.02950210005002. PMID:13221413.
[18] Davignon A, Larieux G, Genest J. Chlorpromazine in the treatment of stubborn hiccup. Union Med Can. 1955;84:282.
[19] Wang J, Zhu Q, Zhang S, Wen L, Wang L. Observation of clinical efficacy of anisodamine and chlorpromazine in the treatment of intractable hiccup after stroke. Bio Med Research International. 2022; Article ID 6563193.10 pages. Doi: https://doi.org/10.1155/2022/6563193. PMID:35915796.
[20] Rajagopalan V, Sengupta D, Goyal K, Dube SK, Bindra A, Kedia S. Hiccups in neurocritical care. J Neurocrit Care. 2021;14(1):18-28. Doi: https://doi.org/10.18700/jnc.200018.
[21] Conley RR, Meltzer HY. Adverse events related to olanzapine. J Clin Psychiatry. 2000;61(Suppl 8):26-29; discussion 30. PMID: 10811240.
[22] Stav A, Weksler N, Berman M, Lemberg L, Ribak L, Segal A, et al. Premedication with metoclopramide decreases the frequency of methohexital induced hiccup. J Anesth. 1992;6:17-20.

**PARTICULARS OF CONTRIBUTORS:**
1. Junior Resident, Department of Anaesthesia, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
2. Professor, Department of Anaesthesia, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
3. Professor, Department of Anaesthesia, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
4. Associate Professor, Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
5. Assistant Professor, Department of Anaesthesia (Trauma), Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.
6. Professor, Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Sarita Kumari,
Assistant Professor, Department of Anaesthesia (Trauma Centre), Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, Uttar Pradesh, India.
E-mail: drsarita.anesthesia@gmail.com

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