

Comparative Study of Multimodal Analgesia and Morphine Analgesia Concerning the Adverse Effects Following Open-Heart Surgeries

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ABSTRACT

Background: Historically, pain management has been based on opioid analgesics after cardiac surgeries. Opiates, however, have adverse dose-related side effects that have an impact on the recovery of patients. So, evidence-based opioids that spare multimodal analgesia are progressively being used.

Objective: To determine if the multimodal opioid-sparing treatment of dexamethasone, gabapentin, ibuprofen, ketorolac, and paracetamol had fewer side effects and was safe following open-heart surgeries compared to morphine.

Patients and Methods: This prospective, double-blinded randomized, and controlled clinical study was performed on 60 patients scheduled for elective open-heart surgeries with sternotomy at Sohag University Hospital they were randomly allocated into two equal groups, 30 patients each in the Cardiothoracic Department, Sohag University.

Results: Fewer side effects occurred in patients in the multimodal group than in the morphine group. There was nausea and constipation in patients on the morphine versus multimodal group (21 versus 0) with a ratio of 70% (p-value 0.001). Vomiting occurred in patients in the morphine group (12 versus 4) relative to the multimodal group with a ratio of 40% (p-value 0.020). Postoperative creatinine value showed no statistically significant difference in values between the two groups in all days, with the exception of day zero, showing lower values in the multimodal group creatinine level (0.82 ± 0.25 versus 1.02 ± 0.28 in morphine group (p-value 0.006).

Conclusions: The multimodal regimen offered lower side effects than morphine group in patients undergoing cardiac surgery. There dramatically decreased complaint of nausea, vomiting, constipation, and respiratory depression. In terms of renal complication, no safety issues were found with the multimodal regimen.

Keywords: Multimodal analgesia, Open-heart surgeries, NSAIDs, Gabapentin, Morphine.

INTRODUCTION

Heart and/or the proximate large vessels surgery is known as a cardiac surgery. It is also a procedure intended to enhance the quality of life. It is performed under anesthesia and can be performed either laparoscopically or as open-heart surgery ⁽¹⁾.

The best method for direct visualization of the heart and the related viscera is median sternotomy. Median sternotomy involving cardiac surgery requires coronary artery bypass grafting, replacement of valves and reconstruction of a number of congenital cardiac diseases ⁽²⁾.

Sternotomy causes important postoperative pain in cardiac surgery, which has both major short-term and long-term effects. Acute postoperative pain that is poorly controlled can complicate the immediate postoperative period and can cause chronic pain as well ⁽³⁾. Many unfavorable problems may result from inadequate analgesia in the postoperative period, hemodynamic instability (hypertension, tachycardia, and vasoconstriction), immunological disorder (impaired immune response), metabolic disorder (extensive catabolism) and hemostatic disorder (platelet activation) ⁽⁴⁾. Consequently, adequate analgesia during the postoperative period will potentially minimize morbidity, and improve the quality of life ⁽⁵⁾.

A multimodal opiate sparing regimen composed of dexamethasone, gabapentin, NSAIDs such as ibuprofen, ketorolac, and paracetamol is the justification for the administration of various analgesics, not only the opioid sparing effect, but also the achievement of more efficient pain relief to minimize opioid side effects and enhance pain ratings ⁽⁶⁾. Nonsteroidal anti-inflammatory agents (NSAIDs) are effective in decreasing the amount of opiates requested and offered to patients, thus reducing side effects of opioids. They act by blocking the development of prostaglandins by inhibiting the enzyme cyclooxygenase (COX), resulting in an anti-inflammatory response ⁽⁷⁾.

Gabapentin is an analogue of gamma-aminobutyric acid (GABA), and is primarily used for the treatment of epilepsy and neuropathic pain, but recently it has been used as part of multimodal regimens following non-cardiac surgery in recent years. By binding to the second subunit of voltage-sensitive calcium channels (alpha2 delta subunit), as well as having a central antiallodynic effect. Gabapentin exerts an anti-nociceptive effect ⁽⁸⁾. Sedation and dizziness, headache, and ataxia were the main side effects reported with gabapentin ⁽⁹⁾.



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Dexamethasone corticosteroid has anti-inflammatory effects. In clinical trials, small doses of dexamethasone showed improved recovery of patients after surgery, especially by reducing fatigue, nausea, and vomiting complaints⁽¹⁰⁾.

Aim of the work was to determine if the multimodal opioid-sparing treatment of dexamethasone, gabapentin, ibuprofen, ketorolac, and paracetamol had fewer side effects and was safe following open-heart surgeries compared to morphine.

PATIENTS AND METHOD

This prospective, double-blinded randomized, and controlled clinical study was performed on 60 patients scheduled for elective open-heart surgeries with sternotomy at Sohag University Hospital. They were randomly allocated into two equal groups, 30 patients each in the Cardiothoracic Department of Sohag University.

Ethical consideration: This work was approved by the Ethical and Research Committee of Sohag Faculty of Medicine and a written informed consent was obtained from each patient prior to participation.

Criteria for inclusion: Age > 18 years and any sternotomy-related cardiac operations.

Criteria for exclusion: Peripheral neuropathy, neurological disorder, psychological diseases, history of GI bleeding, persistent pain (i.e. back pain, cancer, arthritis), serum creatinine >150 mmol/l, a hepatic disease with elevated liver enzymes (SGPT and SGOT increased to 1.5 times the overall normal value) and allergy to opioid or drugs of research misuse.

Preparation of the patients: Pre-anesthetic checkup and pre-anesthetic tests such as full blood count, bleeding time, prothrombin time and concentration, activated partial thromboplastin time, liver and kidney function tests, random blood sugar, hemoglobin1c, ECG, cardiac catheterization, coronary angiography, and carotid doppler were carried out to all patients.

Monitoring of the patients: It requires monitoring of five leads electrocardiography (ECG), 20-gauge radial intra-arterial cannula for invasive monitoring of blood pressure, central venous pressure (CVP) via the internal jugular vein, pulse oximetry, non-invasive monitoring of blood pressure and nasopharyngeal temperature monitoring.

There are two groups in the study: **Group I** (multimodal analgesia) where dexamethasone, ketorolac, gabapentin, ibuprofen, and paracetamol were administered to patients. **Group II**, where morphine was administered to patients.

Analgesic protocol (intervention):

Preoperatively: the following were given to patients:

- One hour before surgery, 3 mg of midazolam IV was given to patients of both groups
- Two hours before surgery, 300 mg of gabapentin was given to patients in (Group I).

Group I: the following were administered to patients:

- 300 mg of gabapentin by mouth, 2 hours before surgery.
- 30 mg of ketorolac and 8 mg of dexamethasone IV, along with 1 g of paracetamol IV in the ICU before patient extubation.
- One hour after extubation of patients, 300 mg of gabapentin by mouth and 1 g of paracetamol IV.
- 300 mg of gabapentin daily every 12 hours orally, 400 mg of ibuprofen orally, and 1 g of paracetamol daily IV every 6 hours, from the first to the fourth postoperative day.

Group II: the following were administered to patients:

- Upon arrival at the ICU, 5 mg of morphine IV bolus was authorized for further administrations of up to a total of 25 mg⁽¹¹⁾.
- 2.5 mg of morphine daily every 6 hours from the first to the third postoperative day.
- 1.25 mg of morphine daily every 6 hours on the fourth postoperative day.

In both groups: the following were administered to patients:

- For pain relief, NSAID such as Ibuprofen 400 mg oral or ketorolac 30 mg IV was permitted to be given to patients by the attending nurse and morphine was given as an injection of 2.5-5 mg IV if NSAIDs was ineffective.
- 4 mg ondansetron IV, and/or 10 mg of metoclopramide IV daily every 8 hours, 40 mg pantoprazole once daily, and 1 g of magnesium oxide once daily rectally to alleviate relief of nausea and constipation.

Statistical analysis

Prior to further statistical analysis, the data were tested for normality using the Kolmogorov-Smirnov test and for homogeneity variances. Number and percent described categorical variables, while the mean and standard deviation (Mean, SD) described continuous variables. Chi-square was used to compare between categorical variables, while t-test was used to compare between continuous variables. $P \leq 0.05$ has been found to be statistically significant. IBM SPSS program version 20.0 was used to conduct all the analyses. Data entry and analysis were conducted blinded to group allocation.

RESULTS

In our study, 60 patients were scheduled for elective open-heart surgery such as valve replacement or valve repair, ASD repair and CABG with sternotomy. They were divided into two equal groups, 30 patients in each group.

Demographic data.

Age, sex, weight, height, and BMI were compared and presented in (table 1) as mean ± standard deviation. There was a statistically significant difference in age, weight, and BMI, while there was no statistically significant difference in sex and height values between the two groups.

Table (1): Demographic data

Demographic data	Multimodal (n=30)		Morphine(n=30)		P. value
	No.	%	No.	%	
Age in years	39.2 ± 14.31		48.57 ± 14.54		0.015*
Sex					
Male	13	43.3	19	63.3	0.121
Female	17	56.7	11	36.7	
Weight in kg	64.43 ± 16.51		72.77 ± 12.37		0.031*
Height in cm	1.64 ± 0.12		1.65 ± 0.09		0.770
BMI	23.57 ± 3.56		26.81 ± 4.52		0.003**

* Statistically significant difference (p<0.05),

**Highly statistically significant difference (p<0.01)

Detection of the side effects of the medications by the daily questionnaire:

Nausea, vomiting, pruritus, sedation, and respiratory depression showed statistically significant differences in values between both groups (being lower in the multimodal group). With the exception of hallucination, mental instability, and dizziness, there was no statistically significant differences between the two groups. On the fourth day after surgery, hallucination was observed in one patient in the multimodal group, and gabapentin was stopped, which led to normalization of the conscious level in one day (Figure 1).

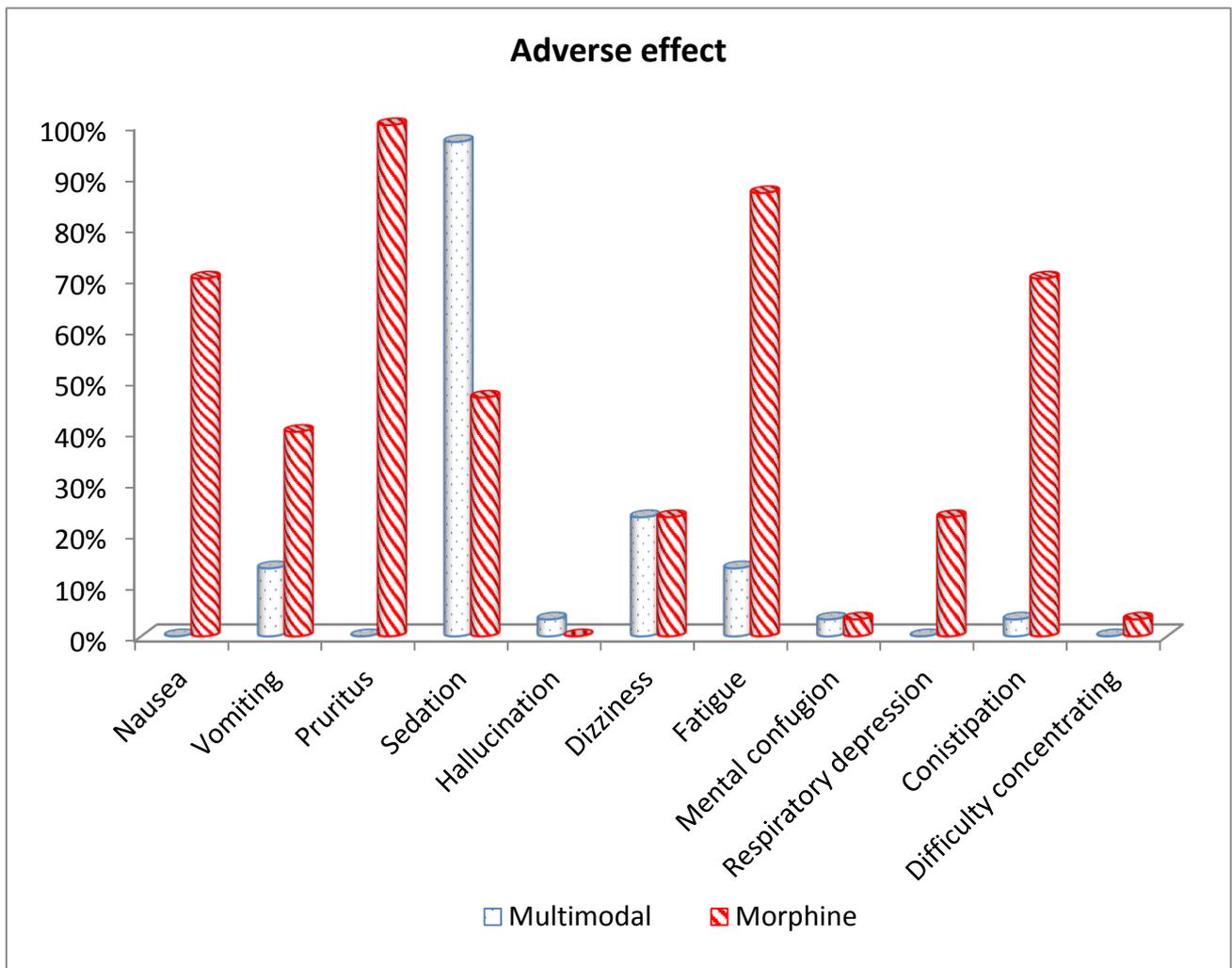


Figure (1): Adverse effects of medications

The Ramzy sedation score for evaluation of sedation caused by drugs:

There was statistically significant difference between both groups with 70% of cases with score 2 in the multimodal group and with 10.0% of cases in the morphine group (p< 0.001) (Table 2).

Table (2): Ramzy sedation score

	Multimodal (n=30)		Morphine (n=30)		P-value
	No.	%	No.	%	
RAMZY score					
Score 1	1	3.3	16	53.3	<0.001**
Score 2	21	70.0	3	10.0	
Score 3	7	23.3	6	20.0	
Score 4	1	3.3	5	16.7	

(P-value) calculated by using Chi-square, Independent-samples t Test **Highly statistically significant difference (p<0.01)

The identification of renal complications:

Renal dialysis had occurred in one patient in the multimodal group (3.3%) and one patient in the multimodal group had to undergo hemodialysis after one weak postoperative after renal impairment and renal failure (3.3%) with p-value of 0.313 (Table 3).

Table (3): Renal complication

Complication	Multimodal		Morphine		P-value
	No.	%	No.	%	
Renal impairment failure					
No	2	96.	3	100.	0.313
Yes	1	3.3	0	0.0	
Dialysis					
No	2	96.	3	100.	0.313
Yes	1	3.3	0	0.0	

Pre and postoperative creatinine:

Table (4) showed statistically significant difference in values between both groups in preoperative creatinine level (mg/dl). However, there was no statistically significant difference between both groups in all days except on day zero, which showed statistically significant difference (being lower in the multimodal group) in creatinine level with 0.82 ± 0.25 in the multimodal group and 1.02 ± 0.28 in morphine group (p- 0.006).

One patient in the multimodal group had to undergo hemodialysis after one weak postoperative after renal impairment and failure with a percentage of 3.3 (p-0.313).

Table (4): Pre and postoperative creatinine (mg/dl)

Preoperative and post-operative creatinine	Multimodal (n=30)	Morphine (n=30)	P. value
	Mean ± SD	Mean ± SD	
Pre-operative creatinine			
Zero	0.77 ± 0.28	0.98 ± 0.23	0.003**
Post-operative creatinine			
Day zero /Times			
Zero	0.82 ± 0.25	1.02 ± 0.28	0.006**
Day 1/Times			
Zero	1.03 ± 0.18	1.03 ± 0.18	1.000
Day 2/Times			
Zero	0.93 ± 0.25	1 ± 0	0.155
Day 3/Times			
Zero	0.97 ± 0.18	0.97 ± 0.18	1.000
Day 4/Times			
Zero	1 ± 0	0.97 ± 0.18	0.321

Data are expressed as **mean ± standard deviation.** (p-value) was calculated by using **Independent-samples T Test** **Highly statistically significant difference (p<0.01)

DISCUSSION

In our study, sixty patients were scheduled for elective open-heart surgeries such as valve replacement or repair, ASD repair in patients more than 18 years old and CABG. They were allocated in two equal groups, thirty patients in each group.

Group I: Patients who received multimodal analgesia (dexamethasone, ketorolac, gabapentin, ibuprofen and paracetamol).

Group II: Patients who received morphine.

In our study, the mean age of the patients was 39.2 ± 14.31 and 48.57 ± 14.54 years in-group I and group II respectively with a significant difference. The sex distribution of the study population showed that there were 13 males and 17 females in the multimodal group compared to 19 males and 11 females in the morphine group. Although there was some difference in the sex distribution between both groups but this was not significant. Regarding the BMI, it was 23.57 ± 3.56 among the multimodal group compared to 26.81 ± 4.52 in the morphine group with a statistically significant difference. In contrast to our study, **Rafiq et al.** (11) compared between a multimodal regimen consisting of dexamethasone, gabapentin, ibuprofen, ketorolac and paracetamol against a traditional opiate based regimen (morphine and paracetamol) on (180) patients after open cardiac surgeries. They found that there was no significant differences between both groups as regards age, sex, and BMI but with much older age population compared to our study.

Regarding the comorbidities, we found significant differences between both groups as regards hypertension, DM, coronary angiography (all were higher among the morphine group) and PHT (with higher PHT level among the multimodal group) but

other items showed no statistically significant differences between both groups. This is in contrast with **Rafiq et al.** ⁽¹¹⁾ who found that there were no significant differences between both groups as regards hypertension, DM, hyperlipidemia, COPD and previous stroke.

As regards the surgical details, we found no statistically significant differences in the values of anesthesia time, cardiopulmonary bypass time and cross clamp time between both groups. This is in agreement with **Rafiq et al.** ⁽¹¹⁾.

As regards the side effect of drugs that were detected by the comprehensive information collected from side effect questionnaires, we found that there were a statistically significant differences in values between both groups (lower in the multimodal group) regarding nausea, vomiting, pruritus, sedation and respiratory depression. While, hallucination, mental confusion and dizziness showed no significant difference in values between both groups. This is coinciding with the study of **Rafiq et al.** ⁽¹¹⁾ who found that 13 patients from 74 patients (17.5%) in the morphine group experienced nausea and vomiting to such a degree, that they had to discontinue their analgesic regimen. It was noted that morphine had a dose-related side effect profile, and it can be argued that we were not able to titrate morphine levels down as they would have ie. if they had used patient administered morphine pumps, when patients experienced side effects. Nonetheless, none of the patients in the multimodal group had such extensive nausea and vomiting symptoms. This was a very convincing and important finding of their study. Single dose dexamethasone has previously been shown to significantly reduce postoperative nausea and vomiting after cardiac surgery, and improve quality of recovery ^(12, 13). In addition, **Rafiq et al.** ⁽¹¹⁾ confirmed the decrease in the incidence of nausea and vomiting in gabapentin-treated patients than opioid treated patients and reported the occurrence of involuntary contraction of the upper extremity in one patient in the multimodal group who led to normalization on stopping of gabapentin regimen in one day. The degree of benefit was not related to the dose of gabapentin, although one randomized controlled trial on lumbar discectomy showed an analgesic ceiling effect at 600 mg. The timing (preoperative versus postoperative), the dose and duration of gabapentin in different studies have been very variable and hence we cannot recommend a particular regimen ⁽¹⁴⁾. In contrast, the study of **Mota et al.** ⁽¹⁵⁾ showed no significant differences between both groups regarding any of the studied complications (nausea, vomiting, pruritus and respiratory depression). Besides, the study of **Soltanzadeh et al.** ⁽¹⁶⁾ found that the incidence of nausea, vomiting and respiratory depression within 24 h were comparable between both groups. Moreover, the study of **Özmen et al.** ⁽¹⁷⁾ showed that there was no statistically significant difference between the groups in terms of nausea or vomiting

severity. The study of **Imantalab et al.** ⁽¹⁸⁾ and **Xiaoxi et al.** ⁽¹⁹⁾ showed that there were no differences regarding nausea, vomiting and hypoxia between both groups.

As regards the assessment of sedation caused by drugs (gabapentin and opioids) by the Ramzy sedation score (RSS), we found that there were a statistically significant differences in values between both groups, 70% with score 2 in the multimodal group and 10.0% in the morphine group ($p < 0.001$). This coincides with the study of **Menda et al.** ⁽²⁰⁾ who found that the number of over sedated patients was significantly higher in the GABA group at 2, 6, and 12 hours compared to placebo with a p value of < 0.001 at 2 and 6 hours and with a p value of < 0.02 at 12 hours, In addition, they reported a significant decrease in the incidence of nausea in gabapentin-treated patients. ($n = 9$) than in the PLA group ($n = 18$) with a p value of 0.02. In contrast, the study of **Altun et al.** ⁽²¹⁾ found that the RSS scores of patients receiving combination of tramadol + paracetamol were lower within the first hours postoperatively. The RSS scores were also higher at the 1st, 2nd, 4th, 8th, 12th, and 30th hours in the placebo group versus the tramadol group ($p = 0.01$ and 0.05 respectively). In all other time points, there was no difference in the RSS scores between the groups.

As regards the detection of the renal complications by follow up of the serum creatinine, we found that there were no statistically significant differences in values between both groups. One patient in the multimodal group had to undergo hemodialysis after one weak postoperative after renal impairment and renal failure after he had been shocked and anuric (3.3% of cases with $p = 0.313$). This is in agreement with **Rafiq et al.** ⁽¹¹⁾ who found that renal complications were not significantly higher in the multimodal group. However, there was a trend towards patient in the multimodal group having greater increase in creatinine levels postoperatively. Furthermore, four patients from 77 patients (5.2%) in the multimodal group had their analgesic regimen stopped by the attending surgeon because of concerns of rising creatinine levels. In contrast, **Qazi et al.** ⁽²²⁾ compared between opioid (oxycodone 10 mg twice) versus NSAIDs (ibuprofen 800 mg twice combined with lansoprazole) with paracetamol in both after cardiac surgery. They found an increased risk of renal impairment using ibuprofen-based regimen than when compared to using oxycodone-based regimen. The rise in serum creatinine was seen within two or three days after surgery, which could indicate that renal impairment occurred prior to this because the time was taken for serum creatinine accumulation. The results of this study could suggest that ibuprofen might act as an aggravating factor in the early postoperative treatment. Adding to the multifactorial genesis of renal failure that short-term use of NSAIDs (ibuprofen) is safe as regards the renal complication with close monitoring of serum creatinine.

Regarding the postoperative creatinine values, we found no significant differences in values between both groups in all days except on day zero, which showed a significant rise of serum creatinine among the morphine group (1.02 ± 0.28 mg/dL) compared to the multimodal group (0.82 ± 0.25 mg/dL) with p-value of 0.006. In contrast, the study of **Qazi et al.** (22) showed that there were no significant difference between both groups in serum creatinine all over the study time periods, except on days 2, 3 and 5 where the opioid group showed significantly lower creatinine level. They also, found a significantly higher serum creatinine in the ibuprofen group on days two, three and five postoperatively. The levels of creatinine increased in nine patients in the ibuprofen group, compared to three in the oxycodone group, this increase in creatinine was by > 50% above the preoperative level within the first 6 days after surgery corresponding to "Risk" in the RIFLE classification. A further nine patients in the ibuprofen group experienced a doubling of their preoperative creatinine corresponding to an acute renal "Injury" in the RIFLE classification. These nine patients all returned to values below the double preoperative creatinine level within 5-13 (mean 9) days after surgery. None of the patients required dialysis of any form.

CONCLUSION

A multimodal treatment consisting of dexamethasone, gabapentin, ibuprofen, and paracetamol offered lower side effects in patients undergoing open-heart surgery than a regimen consisting of morphine. In addition, in the multimodal group, nausea and vomiting symptoms were decreased significantly. While, no increase in individual levels of creatinine in the multimodal group and no dialysis safety concerns were observed. Based on the data, the authors concluded that using non-opioid pain control approaches, generally improved patients. Non-opioid analgesics can be claimed to be a more patient-friendly pain control approach than commonly used opioids.

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