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Surgical timing in neonatal brachial plexus palsy: A PRISMA-IPD systematic review

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Abstract

Background: Neonatal brachial plexus palsy (NBPP) is a serious complication of high-risk deliveries with controversy surrounding timing of corrective nerve surgery. This review systematically examines the existing literature and investigates correlations between age at time of upper trunk brachial plexus microsurgery and surgical outcomes.

Methods: A systematic screening of PubMed, Cochrane, Web of Science, and CINAHL databases using PRISMA-IPD guidelines was conducted in January 2020 to include full-text English papers with microsurgery in upper trunk palsy, pediatric patients. Spearman rank correlation analysis and two-tailed t-tests were performed using individual patient data to determine the relationship between mean age at time of surgery and outcome as determined by the Mallet, Medical Research Council (MRC), or Active Movement Scale (AMS) subscores.

Results: Two thousand nine hundred thirty six papers were screened to finalize 25 papers containing individual patient data (n = 256) with low to moderate risk of bias, as assessed by the ROBINS-I assessment tool. Mallet subscore for hand-to-mouth and shoulder abduction, AMS subscore for elbow flexion and external rotation, and MRC subscore for elbow flexion were analyzed alongside the respective age of patients at surgery. Spearman rank correlation analysis revealed a significant negative correlation ($\rho = -0.30$, p < .01, n = 89) between increasing age (5.50 ± 2.09 months) and Mallet subscore for hand-to-mouth (3.43 ± 0.83). T-tests revealed a significant decrease in Mallet hand-to-mouth subscores after 6 months (p < .05) and 9 months (p < .05) of age. No significant effects were observed for Mallet shoulder abduction, MRC elbow flexion, or AMS elbow flexion and external rotation.

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Conclusion: The cumulative evidence suggests a significant negative correlation between age at microsurgery and Mallet subscores for hand-to-mouth. However, a similar correlation with age at surgery was not observed for Mallet shoulder abduction, MRC elbow flexion, AMS external rotation, and AMS elbow flexion subscores.

1 | INTRODUCTION

Upper trunk NBPP (neonatal brachial plexus palsy) is the most common type of NBPP, found in 46% of neonatal patients with brachial plexus palsy (Ruchelsman et al., 2009). Although studies suggest that most patients experience gradual spontaneous recovery, challenges exist in effectively diagnosing newborns who have low potential for spontaneous recovery and require surgery. Although there are no Level 1 evidence-based studies investigating surgical treatment of NBPP against spontaneous recovery in a randomized manner, poor functional outcomes of spontaneous recovery have been found in NBPP patients (Pondaag & Malessy, 2014). Thirty percent of patients are unable to fully recover through a conservative approach and require surgical repair, including primary and secondary surgeries (Socolovsky et al., 2016). For this reason, many surgeons have recommended early microsurgical nerve repair for severe brachial plexus palsy (Chuang & Ma, 2004).

Multiple authors have suggested that age at NBPP surgery can affect patient outcomes and have given recommendations of appropriate timing for nerve surgery. Gilbert and Tassin recommend that a patient should be indicated for surgery if there is no elbow flexion at 3 months of age (Gilbert & Tassin, 1987). Clarke and Curtis recommend that the indication for brachial plexus exploration is the failure to perform the "cookie test," a test of active biceps function at 9 months of age (Clarke & Curtis, 2001). Chuang et al. recommend brachial plexus exploration if there is still no elbow flexion at 6 months of age (Chuang & Ma, 2004). However, if there is still poor shoulder or elbow function, there is a continued indication for exploration after 1 year of age (Chuang & Ma, 2004).

Timing of surgery for NBPP remains controversial with no clear consensus on the optimal age. A multicenter study by Bauer et al. concluded that early NBPP surgery at a mean age of 4.2 months does not correlate with improved surgical outcomes as determined by Active Movement Scale (AMS) scores when compared to delayed surgical age at a mean age of 10.7 months (Bauer et al., 2020). Currently, there is no study that utilizes a systematic review to determine the most effective timing of microsurgery for upper trunk NBPP in pediatric patients.

In this article, we systematically review evidence behind timing for successful microsurgery and present upper limits for when surgery can be attempted with satisfactory outcomes to aid in the decision making process of determining timing of nerve microsurgery.

2 | MATERIALS AND METHODS

2.1 | Literature search

A systematic search of the PubMed. Cochrane. Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases was conducted, and articles from 1970 to January 2020 were screened using Preferred Reporting Items for Systematic Reviews and Meta-Analysis Individual Patient Data (PRISMA-IPD) guidelines (Moher et al., 2009). Boolean searches were performed with terms related to "brachial plexus palsy," "pediatric," and "surgery." Exclusion criteria and the step-wise process of the screening are detailed in Figure 1. Inclusion criteria consisted of full text English articles, including patients under 18 years of age with upper trunk (C5-C6 or C5-C7) neonatal brachial plexus microsurgery (nerve grafts, nerve transfers, neurorrhaphy, and/or neurolysis) with clear surgical outcomes for each patient. References of all the full text studies were crosschecked for inclusion. The initial review was performed by three independent authors (Nivetha Srinivasan, Jasmine Mahajan, Shivani Gupta), and disagreements were solved through discussion with principal investigators (Aleksandra McGrath and Alice Chu).

2.2 | Data extraction and further screening

Data extracted from each study included year of publication, study type, number of patients, age at surgery (mean, median, range, and/or individual data points), levels of brachial plexus lesions, mean follow-up, and type of outcome (Mallet hand-tomouth and shoulder abduction (Al-Qattan & El-Sayed, 2014a; Mallet, 1972), Medical Research Council (MRC) elbow flexion (Bhardwaj & Bhardwaj, 2009; Medical Research Council, 1943), or AMS external rotation and elbow flexion subscores (Curtis et al., 2002). The database created from this extraction process was used to identify papers including patients with upper trunk brachial plexus palsy, defined as C5–C6 or C5–C7. Papers that did not have the aforementioned subscores were excluded, except those that were later converted: Gilbert scores and range of motion (ROM) in degrees. Papers with modified MRC and British MRC were pooled with papers using MRC.

Papers that included individual data points for age and outcomes of interest were included in the final analysis. Additional individual data points from papers with upper plexus palsy NBPP patients were requested from authors of these studies. FIGURE 1

patient data



2.3 Score conversions

Papers that included Gilbert shoulder abduction subscores were converted to Mallet shoulder abduction subscores. Conversion was conducted as follows: Angles of shoulder abduction less than 30° (Mallet grade 2), angles between 30° and 90° (Mallet grade 3), and angles greater than 90° (Mallet grade 4) (Al-Qattan & El-Sayed, 2014a; Mallet, 1972). For example, a Gilbert shoulder abduction subscore of 5 corresponds to active abduction greater than 120°, which is then converted to a Mallet score 4.

Active ROM was converted to Mallet scale based on the original publication by Mallet (Mallet, 1972). Active ROM was converted to AMS scale based on the publication by Curtis et al. (Curtis et al., 2002). The conversion of ROM to a scale subscore was done on a case-by-case basis, taking into account the scale utilized in the paper. It is to be noted that Mallet (scored 2-4) is considered a more coarse outcome measure than MRC (scored 0-5), which is more coarse than AMS (scored 0-7) in regards to level of classification of joint motion. Thus, careful consideration was taken during ROM conversions to prevent inaccurate extrapolation of data to AMS scale subscores.

2.4 Statistical analysis

Quantitative synthesis was performed using extracted individual data points from the finalized papers. Analysis with Spearman rank correlation coefficient (ρ) was conducted at α = 0.05 to determine if there was any

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TABLE 1 Summary of included studies with Mallet subscores

Study	Study type	Subscore	No. of Pts	Age in months (mean)	Mallet subscore (mean)
Xu et al., 2000 (Ghanghurde et al., 2016)	Prospect comp	Shoulder abduction	8	4.9	3.1
		H-to-M	8	4.9	3.1
Blaauw & Slooff, 2003 (Gibon et al., 2016)	Retro OS	H-to-M	21	3.7	3.6
Grossman et al., 2004 (Azzi et al., 2018) ^a	Retro OS	Shoulder abduction	7	14.4	3.9
Terzis & Kostas, 2005 (Meyer, 1986)	Retro case series	Shoulder abduction	1	5	4
Blaauw et al., 2006 (Grossman et al., 2004)	Retro OS	Shoulder abduction	2	5.7	2.5
		H-to-M	2	5.7	3.5
Terzis & Kostas, 2008 (Noaman et al., 2004)	Retro OS	Shoulder abduction	2	3.1	3
Gosk et al., 2010 (Chuang et al., 2005) ^a	Retro comp	Shoulder abduction	5	4	3.2
Malessy & Pondaag, 2014 (Terzis & Kostas, 2005)	Retro OS (Level III)	Shoulder abduction	34	5.7	3.6
		H-to-M	34	5.7	3.3
Ghanghurde et al., 2016 (Terzis & Kostas, 2008)	Retro OS	Shoulder abduction	17	5.8	3.1
		H-to-M	17	5.8	3.1
Gibon et al., 2016 (Gosk et al., 2010)	Retro OS	Shoulder abduction	7	5	3.4
		H-to-M	7	5	4.6
Azzi et al., 2018 (Lin et al., 2011) ^b	Retro OS	Shoulder abduction	8	8.0	3.3

Abbreviations: Comp, comparative study; H-to-M; hand-to-mouth; NA, not available; No., number; OS, observational study; prospect, prospective; Pts, patients; Retro, retrospective.

^aIndicates article that was converted from Gilbert to mallet scale.

^bIndicates article that was converted from ROM to mallet scale.

TABLE 2 Summary of included studies with MRC subscores

Study	Study type	Subscore	No. of Pts	Age in months (mean)	MRC subscore (mean)
Meyer, 1986 (Luo et al., 2011)	Retro OS	Elbow flexion	3	4.7	2.7
Xu et al., 2000 (Ghanghurde et al., 2016)	Prospect comp	Elbow flexion	8	4.9	3.6
Noaman et al., 2004 (Siqueira et al., 2012)	Retro case series	Elbow flexion	7	15.4	3.3
Chuang et al., 2005 (Al-Qattan & Al-Kharfy, 2014)	Retro OS	Elbow flexion	4	22.8	3.8
Lin et al., 2011 (Little et al., 2014)	Retro OS	Elbow flexion	15	7.5	2.9
Luo et al., 2011 (Mencl et al., 2015)	Retro comp (Level III)	Elbow flexion	8	7.9	3.7
Siqueira et al., 2012 (Argenta et al., 2016)	Prospect OS	Elbow flexion	16	13	3.4
Malessy & Pondaag, 2014 (Terzis & Kostas, 2005)	Retro OS (Level III)	Elbow flexion	34	5.7	4.1
Ghanghurde et al., 2016 (Terzis & Kostas, 2008)	Retro OS (Level IV)	Elbow flexion	17	5.8	4
Gibon et al., 2016 (Gosk et al., 2010)	Retro OS	Elbow flexion	7	5	3.4

Abbreviations: Comp, comparative study; H-to-M; hand-to-mouth; MRC, Medical Research Council; NA, not available; No., number; OS, observational study; prospect, prospective; Pts, patients; Retro, retrospective.

relationship between age and surgical outcome. Unpaired t-tests were also performed for each outcome measure with n > 3 with age cutoffs of 3, 6, 9, and 12 months. A value of p < .05 was considered statistically significant. Simple linear regression was used to predict surgical outcomes from age and follow-up months. Data analysis was completed with the statistical package SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

After removing duplicates, 2936 unique papers were identified (Figure 1). A total of 25 papers containing 256 individual patient data points were included in the analysis.

3.1 | Review characteristics

The 25 publications included in our review were retrospective observational studies published between 1986 and 2016 with the majority after 2010. The mean age of all included patients was 11.4 ± 10.7 months (range 2.5–65 months). The range of average follow-up time for these patients was 7–216 months. Tables 1, 2, and 3 detail the characteristics of the outcome subscores. Microsurgeries performed in these studies include proximal and distal nerve grafts, nerve transfers, neurolysis, neurorrhaphy, or a combination of these microsurgical procedures. Individual ages, outcomes, and procedures of all 256 patients can be found in supplemental Table 1.

TABLE 3 Summary of included studies with AMS subscores

Study	Study type	Subscore	No. of Pts	Age in months (mean)	AMS subscore (mean)
Al-Qattan & Al-Kharfy, 2014 (Figueiredo Rde et al., 2016)	Retro OS	Elbow flexion	10	14.7	6.2
Bade et al., 2014 (Chuang, 2016)	Retro OS	External rotation	10	10.2	3.7
Little et al., 2014 (Murison et al., 2017)	Retro OS (Level IV)	Elbow flexion	17	10	5.9
Mencl et al., 2015 (Semaya et al., 2019)	Retro OS	External rotation	11	5.3	5.4
		Elbow flexion	11	6.2	6.2
Argenta et al., 2016 (Bade et al., 2014)	Retro OS	External rotation	5	10.8	6.6
		Elbow flexion	5	10.8	6.8
Figueiredo Rde et al., 2016 (Jivan et al., 2006)	Retro OS	Elbow flexion	13	12	4.5
Murison et al., 2017 (Birch, 2015)	Retro OS	Elbow flexion	9	13.4	5.7
Semaya et al., 2019 (Jivan et al., 2009)	Prospect OS	Elbow flexion	16	40.6	5.6

Abbreviations: AMS, Active Movement Scale; Comp, comparative study; H-to-M; hand-to-mouth; NA, not available; No., number; OS, observational study; prospect, prospective; Pts, patients; Retro, retrospective.

3.2 | Risk of bias and quality of evidence

Risk of bias was assessed by authors using the Risk of Bias in Non-Randomized Studies- of Interventions (ROBINS-I) assessment tool in a similar manner as article screening (Sterne et al., 2016). If a study included individual patients who received secondary surgeries or botulinum toxin, these patients were removed from analysis and were not considered when completing the bias assessment.

Overall, there was a low to moderate risk of bias across the 25 studies included in this review (Figure 2) (McGuinness & Higgins, 2020). Most papers had low bias due to confounding but showed serious bias in selection of the reported results. This was due to reporting of multiple outcome measurements within the same outcome domain or due to different subgroups.

3.3 | Outcomes as assessed by spearman rank correlation

Spearman rank correlation revealed a moderate, negative monotonic correlation ($\rho = -0.30$, n = 89, p < .01) between increasing age (5.50 ± 2.09 months) and Mallet subscore for hand-to-mouth (3.43 ± 0.83) (Blaauw et al., 2006; Blaauw & Slooff, 2003; Ghanghurde et al., 2016; Gibon et al., 2016; Malessy & Pondaag, 2014; Xu et al., 2000). There was no significant correlation between age (6.31 ± 3.33 months) and Mallet subscore for shoulder abduction (3.41 ± 0.82, $\rho = -0.09$, n = 91, p = .41) (Azzi et al., 2018; Blaauw et al., 2006; Ghanghurde et al., 2016; Gibon et al., 2016; Gosk et al., 2010; Grossman et al., 2004; Malessy & Pondaag, 2014; Terzis & Kostas, 2005; Terzis & Kostas, 2008; Xu et al., 2000) or between age (7.92 ± 5.62 months) and MRC subscore for elbow flexion (3.65 ± 0.79, $\rho = -0.10$, n = 119, p = .29) (Chuang et al., 2005; Ghanghurde et al., 2016; Gibon et al., 2016; Lin et al., 2011; Luo et al., 2011; Malessy & Pondaag, 2014; Meyer, 1986; Noaman et al., 2004; Siqueira et al., 2012; Xu

et al., 2000). There was also no significant correlation between age (16.85 ± 13.93 months) and AMS subscore for elbow flexion (5.72 ± 1.76, $\rho = -0.16$, n = 81, p = 1.14) (Al-Qattan & Al-Kharfy, 2014; Argenta et al., 2016; Figueiredo Rde et al., 2016; Little et al., 2014; Mencl et al., 2015; Murison et al., 2017; Semaya et al., 2019) and between age (10.37 ± 0.82 months) and AMS subscore for external rotation (4.96 ± 1.95, $\rho = -0.04$, n = 26, p = .84) (Argenta et al., 2016; Bade et al., 2014; Mencl et al., 2015).

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3.4 | Outcomes as assessed by t-tests and linear regression

Results of two-tailed unpaired t-tests for outcomes at age cutoffs of 3, 6, 9, and 12 months are provided in Table 4. There was a significant decrease in Mallet hand-to-mouth subscores after the age of 6 months (p < .05) and 9 months (p < .05).

Linear regression analysis for Mallet hand-to-mouth revealed a significant negative relationship between age at surgery and outcome ($R^2 = 0.147, p < .01, n = 89$, Figure 3).

4 | DISCUSSION

This review sheds light on the delicate nature of timing of surgery for NBPP. From a biological perspective, motor neuron death, particularly in preganglionic injuries, can be prevented by early repair (Jivan et al., 2006). The correlation between delay in brachial plexus surgery and poor functional outcomes in adults has been investigated and confirmed (Birch, 2015; Jivan et al., 2009). On the other hand, given the rarity of the diagnosis and small size of the infant, early exploration may be detrimental and potentially morbid (Chuang, 2016). There is a high risk of severe postoperative complications in neonatal surgeries from general anesthesia due to susceptibility to intrapulmonary shunt, oxygen toxicity, and



FIGURE 2 ROBINS-1 risk of bias assessment. ROBINS-1, risk of bias in non-randomized studies of interventions

pulmonary barotrauma (Catré et al., 2013). Correctly diagnosing the injury type is the basis for the current prognostic recommendation for an observation period. However, this waiting period can potentially worsen future recovery in patients with more severe lesions (van Ouwerkerk, 2005). The results of this systematic review suggest a negative correlation between age at brachial plexus microsurgery and Mallet subscores for hand-to-mouth. Hand-to-mouth score is affected by the child's ability to flex the elbow, externally rotate the shoulder, and supinate the forearm. However, this correlation was not observed for

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Results of t-tests at different age cutoff points for each subscore

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TABLE

		Age cutoff (in m	nonths)						
Outcome		≤3	>3	≥6	>6	≤9	->9	≤12	>12
Mallet shoulder abduction	Mean ± SD (n)	3.3 ± 1.4 (8)	3.4 ± 0.8 (83)	3.5 ± 0.8 (60)	3.3 ± 0.9 (31)	3.5 ± 0.8 (77)	3.1 ± 0.9 (14)	3.4 ± 0.8 (85)	3.8 ± 0.4 (6)
	<i>p</i> -value	.7398		.2271		.2264		.413	
Mallet hand-to-mouth	Mean ± SD (n)	3.7 ± 0.5 (6)	3.4 ± 0.8 (83)	3.6 ± 0.8 (69)	3 ± 0.9 (20)	3.5 ± 0.8 (84)	2.2 ± 0.4 (5)	NA	NA
	<i>p</i> -value	.0901		.0181 ^a		.012 ^a		NA	
MRC elbow flexion	Mean ± SD (n)	3.6 ± 0.7 (8)	3.7 ± 0.8 (111)	3.7 ± 0.7 (69)	3.6 ± 0.9 (50)	3.7 ± 0.7 (92)	3.4 ± 1 (27)	3.7 ± 0.7 (100)	3.5 ± 1.1 (19)
	<i>p</i> -value	.9079		.2871		.1314		.4086	
AMS elbow flexion	Mean ± SD (n)	NA	NA	6.1 ± 1.6 (17)	5.6 ± 1.8 (64)	5.9 ± 1.8 (23)	5.6 ± 1.7 (58)	5.7 ± 1.8 (40)	5.7 ± 1.7 (41)
	<i>p</i> -value	NA		.3330		.5398		.9642	
AMS external rotation	Mean ± SD (<i>n</i>)	NA	NA	5.3 ± 1.1 (10)	4.8 ± 2.4 (16)	$5.4 \pm 1 \ (11)$	4.7 ± 2.4 (15)	NA	NA
	<i>p</i> -value	NA		.4250		.3280		NA	
Abbreviations: AMS, Active Mov	vement Scale; MRC, 1	Medical Research (Council; NA, not appli	icable.					

^aIndicates significance (p < .05)

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MRC and AMS subscores for elbow flexion or AMS subscore for external rotation. It is possible Mallet hand-to-mouth indicates superior recovery of supination in children operated at earlier ages. Al-Qattan and his colleagues have found that there can be discrepancies between Mallet shoulder abduction and shoulder external rotation in the same patient. The deltoid, the primary abductor of the shoulder, is innervated by the posterior division of the upper trunk, while the infraspinatus, the primary shoulder external rotator, is innervated by the suprascapular branch of the upper trunk. Therefore, the variable distribution of intrapartum forces on the brachial plexus can explain the differences in the deficits of shoulder abduction and external rotation in the same patient (Al-Qattan & El-Sayed, 2014b).

Our results for Mallet outcomes concur with the existing literature. A systematic review by Pondaag and Malessy comparing nerve reconstruction to conservative treatment for NBPP found that the prospect of positive surgical outcomes decreases with increased delay of surgical age with a probable cut-off point between 3 and 6 months of age (Pondaag & Malessy, 2014). When analyzing correlations with age, Bauer et al's multicenter study looked at AMS hand subscores and total AMS scores (Bauer et al., 2020). Our review showed similar results to Bauer et al. as age was not found to be a significant predictor of surgical outcomes in terms of AMS scale subscores. Other studies have shown that intercostal nerve transfers and neurotization can be attempted in older children until 5-6 years of age (Semaya et al., 2019: Sénès et al., 2015). Our results for Mallet hand-to-mouth subscore indicate that if microsurgery cannot be completed by 6 months of age due to unavoidable circumstances, surgery can possibly be delayed for up to 9 months of age and still provide significant functional improvement in supination.

There is potential for patient severity selection bias due to the retrospective nature of this review as patients operated on earlier may not have had time to recover naturally.

Additionally, there are likely to be variations between surgeons due to the level of experience in navigating more complicated procedures in infants (Pondaag & Malessy, 2014).

Another limitation of this analysis is the heterogeneity of studies included. Analysis of subgroups of patients treated with different surgical techniques could not be performed as many studies did not specify one particular treatment type for individual patients. However, while more proximal nerve grafts and more distal nerve transfers may have a substantial difference in recovery time in adults because of greater difference in the distance to target organs, differences due to location may not have a substantial impact on outcomes for the purposes of this review because children have shorter limbs and thus shorter distance to target organs, regardless of the surgical technique chosen. Furthermore, Chim et al. found no statistical difference in outcome between patients who had nerve grafts and those who had nerve transfers (Chim et al., 2014). During the review process, authors were contacted to obtain de-identified data from studies, but this was unsuccessful due to conditions of institutional review boards. To obtain more robust data to draw conclusions, ethical applications for future studies should include a clause about sharing data for the purpose of systematic reviews.



FIGURE 3 Linear regression analysis for mallet hand-to-mouth subscore and age

Variations in preference of utilizing AMS, MRC, or Mallet scales to report outcomes can possibly be explained by the differences in complexity of performing the evaluation. Mallet outcomes can only be used with older cooperative children due to the level of functional positioning required (Curtis et al., 2002). MRC is limited to one grade for partial movement classification, while AMS has less reliably evaluated upper-extremity movements of forearm pronation and supination (Al-Qattan, 2003). The International Plexus Outcome Study Group determined that active ROM in degrees and Mallet scores should be utilized for when standardization of surgical outcomes in NBPP (Pondaag & Malessy, 2018).

5 | CONCLUSIONS

In upper trunk NBPP, microsurgeries performed before 6 months of age significantly improved outcomes of Mallet subscores for hand-tomouth suggesting that children operated on earlier might have better supination recovery, in the absence of any differences when comparing elbow flexion, shoulder abduction, and shoulder external rotation.

CONFLICT OF INTEREST

The authors report no conflict of interest in regards to the materials, methods used in this review, or findings of this article.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

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