



Pupillary Response to Light is Preserved in Patients without Brain Insult Undergoing Rapid Sequence Intubation

Abhishek Chaturbedi^{1*}, Jitendra Thakur¹, Aashik Jha² and Milan Niraula²

¹Department of Neurosurgery, Manmohan Memorial Medical College and Teaching Hospital, Swoyambhu, Kathmandu, Nepal.

²Department of Emergency Medicine, Manmohan Memorial Medical College and Teaching Hospital, Swoyambhu, Kathmandu, Nepal.

Authors' contributions

This work was carried out in collaboration among all authors. Author AC designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AJ and MN managed the analyses of the study. Author JT managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i930507

Editor(s):

(1) Chan-Min Liu, Xuzhou Normal University, PR China.

Reviewers:

(1) Anton Tkachenko, Kharkiv National Medical University, Ukraine.

(2) A. Sheryl Oliver, St. Joseph's College of Engineering, India.

(3) Ghanshyam Gahlot, Rajasthan University of Health Sciences, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/58680>

Received 25 April 2020

Accepted 30 June 2020

Published 30 June 2020

Original Research Article

ABSTRACT

Objective of the Study: This paper has been aimed to determine whether the pharmacological neuromuscular blockade with rocuronium during emergency Rapid Sequence Intubation (RSI) affected pupillary response to light (PLR) in patients with brain insult as compared to patients who had non- neurological illness. Previous studies elucidated that RSI with pharmacological neuromuscular blockade does not affect PLR, except in patients with significant neurological lesion. Our objective is to examine the validity of existing but scarce literature on this subject, with further stratification of patients involved in this study into neurological and non-neurological disease groups.

Methods: This was a prospective case-reference study of case group with brain insult patients compared with reference group of patients without neurological diseases undergoing RSI in

*Corresponding author: E-mail: abchaturbedi@gmail.com;

emergency settings. It is single centered study, conducted from October 2019 till May 2020. A pair of a neurosurgeon and a medical officer assessed pupillary light response after administration of neuromuscular blockade and intubation, each blinded to other's assessment of PLR. Cases without pupillary response before RSI intubation were excluded. The primary outcome measure was clinically observable Pupillary Light Response (PLR) following neuromuscular blockade with Rocuronium in each group.

Results: We examined 50 patients undergoing RSI with Rocuronium, either in emergency department or Intensive Care Unit (ICU), 25 each in index and reference group respectively. All patients in the reference group showed PLR after RSI. Of case group patients receiving RSI, only 15 of 25 (60%) demonstrated PLR after RSI. This was statistically significant (p value < 0.05) when compared to number of patients with intact PLR after RSI in reference group. Cohen's Kappa Coefficient (k) for inter-observer agreement was 0.70.

Conclusion: Rocuronium does not appear to affect PLR after emergent RSI in patients without brain injury. Only in patients with known brain insult showed impaired PLR, suggesting impaired pupillary light reflex mechanism may be the culprit for this aberration, rather than pharmacological neuromuscular blockade.

Keywords: Pupillary light response; neuromuscular blockade; Rocuronium; rapid sequence intubation; brain injury patients.

1. INTRODUCTION

1.1 Background

Pharmacological neuromuscular blockade using depolarizing agent Succinylcholine or the non-depolarizing agent like Rocuronium to facilitate Rapid Sequence Intubation (RSI) has become routine practice in emergency cases that requires airways to be secured [1]. The effect of these rapid acting neuromuscular blocking agent on pupillary response to light has been questioned for decades. Neurosurgeons are especially skeptical of interpreting PLR in the presence of neuromuscular blockade.

Pharmacological neuromuscular blockage agent include both depolarizing (Succinylcholine) and non-depolarizing (Rocuronium, Vecuronium etc.) agents. Pupillary light response is mediated by ganglionic muscarinic acetylcholine receptors acting on ocular pupillary sphincter muscle, a smooth muscle [2,3]. PLR can be theoretically impaired by both depolarizing and non-depolarizing agents which blocks peripherally located postsynaptic nicotinic acetylcholine receptors [4-6], but may affect centrally located muscarinic and nicotinic acetylcholine receptors [4,6]. The afferent limb of the PLR is mediated by the optic nerve whereas the efferent limb is mediated by the oculomotor nerve. The latter received parasympathetic input from the Edinger-Westphal nucleus located in midbrain which is responsible for contraction of pupillary sphincter muscle, which leads to constriction of pupil when a light is shone to the eye.

Gray et al. verified presence of PLR after the use of non-depolarizing agent (Vecuronium and Pancuronium) in the operating room for nonemergent patients [7]. Caro et al. showed preserved PLR in the majority of the patients undergoing RSI in the emergency setting to the use of paralytics Succinylcholine and Rocuronium [8]. Of the 95 patients in this prospective observational study, 6 did not show PLR. Of these 6 patients which failed to show PLR, 5 had significant neurological injury which was attributed as a potential cause for the lack of pupillary response [8].

1.2 Importance and Objectives of the Study

Clinicians are skeptical of interpreting pupillary light response following administration of pharmacological neuromuscular blocking agents. This is of vital importance to neurosurgeons who use PLR universally to assess neurological status of a patient. They may remain perplexed especially in intubated and paralyzed patients with neurological illness while interpreting PLR. This simple test takes critical significance especially in patients undergoing cranial surgeries who are recovering from paralytics after the surgery or kept paralyzed after operation. If a patient who had intact PLR prior to brain surgery fails to show pupillary response to light after surgery, the neurosurgeon's conundrum is "whether the lack of PLR is due to the paralytic or ongoing brain insult?" This may lead to undue anxiety in neurosurgeons who has to conduct neuro-imaging like Computed

Tomography (CT) scan of the brain to settle the issue at hand.

Gray et al. suggested neuromuscular blockade should not affect pupillary response to light in his study [7]. This study was further collaborated by Caro et al. [8] who showed PLR is not affected following use of a paralytic except in the setting of serious underlying brain insult. We decided to carry out a study primarily aimed at deciphering whether neuromuscular blockade affects PLR. We aimed to provide further robust information to the scant literature available on this subject. We further stratified the subjects into two groups, one with neurological disease and the other with non-neurological disease. All of them had RSI in the emergency settings using Rocuronium as the only paralytic agent. This methodology was adopted to derive valuable information, if any from stratification of the subjects in this study into two distinct groups.

2. MATERIALS AND METHODS

2.1 Study Design

It is a prospective observational study, a case reference study performed in Manmohan Memorial Medical College and Teaching Hospital, Swoyambhu, Kathmandu, Nepal. It is a tertiary care referral center providing emergency care, ICU care and neurosurgical services. Written informed consent was waived for all the subjects. This study is purely an observational study, with no additional financial or emotional burden, no ethical constraint and additional health risk to the patients involved in this study.

We studied 50 consecutive adult patients (older than 18 years) receiving RSI using Rocuronium in critically ill patients between October 2019 and May 2020. Two groups: Case group and Reference group, each with 25 participants (1:1 ratio) were included in this study. Pertinent to mention was that the initial sample size was 100. However, the cause of case exclusion were lack of 2 trained raters at the bedside (n=20), absence of pre-intubation pupillary light response (n=10), missing or incomplete data (n=5), the use of neuromuscular blocking agent other than Rocuronium (n=5), and the emergency nature of the patient precluding protocol completion (n=10). Case group referred to patients with neurological pathology (Table 1). Reference group referred to critically ill patients without neurological diseases (Table 2).

Trained medical officers in critical care carried out RSI using Rocuronium in patients meeting the criteria for this study. Medical officers are practicing physicians who have completed their medical school and licensed to practice medicine, but yet to specialize in a particular field of medicine. Two neurosurgeons and two medical officers who are also the authors in this study performed pupillary light response assessments. All the involved doctors received detailed protocol training encompassing the aim of the study, study design, the approved technique for pupillary assessment and data collection methodology.

For each patient meeting the criteria, the rating physicians was always the pair of a neurosurgeon and a medical officer. The rating physicians independently assessed the patient's PLR before and after neuromuscular blockade administration. The rating physicians were blinded to the other rater's pupillary assessment. The rating physicians were not blinded to the neuromuscular blocking agent given as Rocuronium was the only paralytic approved for this study.

2.2 Exclusion Criteria

Patients were excluded if they did not receive a paralytic for the intubation attempt, if the paralytic used was other than Rocuronium, if pupillary response was absent before rapid sequence intubation, if intubation occurred outside the participating institute, or if the trained raters were not available to carry out the study protocol. If the media of the eye did not allow assessment of pupillary response (example: patients with cataract or corneal opacification), they were excluded from the study. Patients who presented with pinpoint pupils whose pupillary response to light is not discernable was also excluded in this study.

Selection of the sedative, analgesic, use of topical lidocaine spray in the upper airways and laryngoscopy technique was at the discretion of the care team. Immediately after intubation in ED or ICU (within 1-5 minutes), the same rating physicians conducted an independent repeated assessment of pupillary response.

The time sensitive nature of the study required coordinated dual assessment of PLR after paralytic administration. The same pair must be available for both the pre- and post-intubation evaluations.

Table 1. Reason for intubation in reference group

Diagnosis	N (percentage)
Respiratory distress , Not otherwise specified	5(20%)
Exacerbation of Chronic Obstructive Pulmonary Disease	5(20%)
Pneumonia, resulting in acute respiratory distress syndrome	4(16%)
Septic shock following surgical procedures	3(15%)
Diabetic Ketoacidosis	2(8%)
Gastrointestinal bleed, leading to shock	2(8%)
Toxic Ingestion of harmful chemicals	1(4%)
Hepatic Encephalopathy	1(4%)
Eclampsia with co	1(4%)
Pulmonary Embolus causing respiratory distress	1(4%)
Total	25 (100%)

Table 2. Reasons for intubation in case group

Diagnosis	N (percentage)
Spontaneous Intra-cerebral hemorrhage from hypertension	7(28%)
Traumatic Brain Injury with intra-cerebral hemorrhage (ICH)	6(24%)
Traumatic Brain Injury with extra-axial bleeding*	3(15%)
Ischemic Stroke with depressed level of consciousness	3(15%)
Malignant brain infarction syndrome	2(8%)
Diffuse Axonal Injury	2(8%)
Subarachnoid Hemorrhage (SAH) from ruptured brain aneurysm	2(8%)
Total	25 (100%)

**Extra-axial blood in the cranial vault refers to blood between the brain and the skull. It can be subdural hematoma (SDH) or extradural hematoma (EDH)*

2.3 Outcome Measures

The primary outcome was 132apillary response, defined as any constriction (including “brisk” or “sluggish”) occurring after a penlight source challenge. There has to be intact direct and consensual 132 apillary light reflex to light challenge. The independent raters performed all 132apillary assessments with direct observation and challenge with a penlight. We did not use pupilometer to measure 132 apillary response which would have been an ideal study design, but lack of pupilometer in our setting and limited time for pre- and post-intubation precluded its use. We therefore opted for direct observation.

Pupillary response to light is a common assessment tool in patients with traumatic brain injury evaluations, brain insults like intra-cerebral hemorrhage (spontaneous or post traumatic), stroke [4] and brain death assessments [9]. This test has the ability to evaluate extend of brain damage, has prognostication value and in case of brain death, has medico-legal implications.

2.4 Data Collection and Processing

Participating physicians in RSI using Rocuronium completed standard data collection sheets

detailing demographic date, the indication for intubation, and the medications used for RSI and their dosages. Pre- and post-paralysis assessment of pupillary response was recorded by the pair of a neurosurgeon and a medical officer who performed them and were blinded to each other pupillary assessment. Completed data collection forms were placed in a locked data collection box in the neurosurgery department office and were examined on a weekly basis. Any subject whose data collection sheet was incomplete was excluded from the study.

2.5 Primary Data Analysis

We evaluated interrater agreement with Cohen’s *k* [10] and determined the proportion of patients retaining pupillary response after the use of paralytic, calculation binomial proportion with exact 95% confidence intervals (CI). PLR in case and reference groups were evaluated separately. The two groups-case and reference groups were not matched for age and gender. However, other characteristics like the type of paralytic used, the same 4 raters for checking PLR and the technique of RSI were same. Both groups had the same confounding variables like use of

opiates, benzodiazepines and ondansetron. We used IBM SPSS (statistical package for social service) software version 23.0 for statistical analysis. Student's t-test was used to compare mean of two groups in our study to assess their difference.

3. RESULTS

Among 50 patients who underwent RSI, 55 (55%) were men, and the median age was 54 years (interquartile range 18 years to 70 years). In the case group of 25 patients with neurological illness, the median age was 48 years (range: 18-68 years). In the reference group of 25 patients without neurological disease, the median age was 56 years (range: 30-70 years). Both the groups followed normal distribution curve. The age difference between the two groups was not statistically significant (p value >0.05).

Of 25 reference group patients with RSI, all (100%; 95% CI 85% to 100%) had preserved pupillary light reflex after neuromuscular blockade. Of 25 case group patients, 15(60%; 95% CI 52% to 67%) retained pupillary light response after use of the paralytic. The comparison of total number of patients exhibiting PLR after RSI in two groups was statistically significant (p value <0.05). The mean Glasgow Coma Scale (GCS) in the case group with neurological illness was 6 (range 3-10) as compared to mean GCS of 8 (range 5-11) in reference group. The difference in mean GCS between two groups was not statistically significant (p value>0.05). The GCS scale here represents the GCS on hospital arrival.

Out of the 10 cases (Table 3) with neurological diseases with absent pupillary light response, raters agreed on 7 out of 10 patients. In the 10 patients with brain insults which lacked PLR, mean GCS was 5 (range 3-8). The difference in mean GCS between subsets of patients in case group who showed positive PLR after RSI as compared to the ones who did not exhibit it was not significant (p value>0.05). Inter-rater

agreement of pupillary response was good (k=0.70) i.e. Cohen's Kappa coefficient [10].

4. DISCUSSION

Pupillary response to light is an essential component of physical examination especially in critically ill patients with neurological emergencies [11].

Neuromuscular blocking agents are either of depolarizing type (Succinylcholine) or non-depolarizing type (Rocuronium, Vecuronium). The depolarizing and non-depolarizing types cause paralysis of striated muscle by persistent depolarization or competitive blockade of post synaptic nicotinic acetylcholine receptors respectively [5].

The ocular papillary sphincter muscle is composed of smooth muscle, and its neuromuscular endplate is post ganglionic muscarinic acetylcholine receptors type [2,3]. Henceforth, PLR should not be affected by neuromuscular blocking agents when used in patients undergoing RSI.

Gray et al. [7] and Caro et al. [8] showed PLR is preserved in patients undergoing tracheal intubation using RSI with Succinylcholine or Rocuronium with following caveats. The first study was performed in the operating room on non-emergency patients (using paralytics Vecuronium and Pancuronium) while the later was performed in emergency settings (using Succinylcholine and Rocuronium) respectively. Caro et al. [8] found that of 67 patients receiving Succinylcholine, 61 (91%) retained PLR after RSI, while 27 patients receiving Rocuronium, 100% had preserved PLR after paralytic use in their prospective observational study of 95 adult patients. The later showed 5 out of 6 patients showing absent PLR after use of the paralytic had significant neurological injury. The absence of pupillary response was deduced to be due to underlying neurological lesion, rather than the effect of the paralytics.

Table 3. Patients with non-responsive pupils after paralysis

Diagnosis	Rater agreement	N (percentage)
Spontaneous ICH from hypertension	Both in 2 cases*	3(30%)
Traumatic Brain Injury with ICH	Both in 2 cases*	3 (30%)
Traumatic Brain Injury with extra-axial bleeding	Both in 1 case*	2(20%)
Malignant brain infarction syndrome	Both	1(10%)
SAH from ruptured brain aneurysm	Both	1 (10%)
Total	7	10 (100%)

*In remainder case(s), there was discordance between raters as only one rater agreed that there was no PLR after RSI

Our study of 50 adult patients aimed to further selectively dissect the study performed by Caro et al. [8]. We performed a prospective observational study with 2 groups. Critically ill patients with neurological illness (case group) was compared to the patients without neurological illness (reference group) to detect difference in PLR after use of the paralytic Rocuronium. We did not use Succinylcholine as it has the potential to increase intracranial pressure apart from other complications like hyperkalemia. Our study included 25 neurological and non-neurological patients each and we wanted homogeneity of using the same paralytic, hence commonly preferred agent by anesthesiologist Rocuronium was used.

Apart from the use of paralytics that can potentially impairs PLR, other drugs:-sedatives like Midazolam (may affect PLR), opiates like Fentanyl (causes miosis), atropine (mydriasis by parasympathetic blockage) and Ondansetron were used in our study for RSI. Because of the limitation of this study, we cannot ascertain the potential effect of these compounding variables on our results.

We performed the study in emergency settings of critically ill patients in the ED or ICU. We did not perform this study in non-emergency settings like in the operating theater for elective surgeries. Two dedicated physicians trained in critical care performed tracheal intubation using RSI for various medical emergencies, either in ED or ICU. Since this study included neurosurgical patients, the main element of detecting PLR after RSI was always a pair of a neurosurgeon and a medical officer trained in critical care.

In our study, none of the patients in the reference group had absent papillary light response after the use of a paralytic. In contrast, 10 (40%) patients in the case group of critically ill patients with neurological diseases had absent PLR after RSI with Rocuronium, which proved to be statistically significant (p value <0.05) when compared to reference group. These patients (as illustrated in Table 3) had serious neurological injury and pupillary light reflex mechanism may have been impaired by ongoing brain insult. The most likely working explanation is compression of the oculomotor cranial nerve (s) by the lateral or trans-tentorial herniation. Also the rapid rise in intracranial pressure may have significantly reduced central perfusion pressure of the brain, resulting in permanent hypoxic damage to the

brain. This causes diffuse cerebral dysfunction and absent PLR.

Interestingly, there was no statistically significant difference (p value >0.05) in the subset of case group patients who lacked PLR after RSI when their mean GCS was compared to the ones with intact PLR after RSI. This might signify GCS score at presentation to the hospital may not be a reliable indicator to predict which patients will lack PLR after RSI in neurological insult patients. Other factors such as rapidly increasing ICP and evolving brain hematoma with ensuing brain herniation or hypoxic brain damage may be more important factor in predicting loss of PLR. But it begs the question, if ongoing brain insult is happening in real time, fall in GCS should also run in parallel.

In 7 of the 10 patients with lack of post-intubation PLR had effacement of the basal cisterns on Computed Tomography (CT) scan of the brain suggesting lateral brain herniation and brainstem compression. Clinically, 3 out of these 10 patients with absent pupillary response had met the criteria for brain death declaration. Remaining 7 patients had many absent brain stem reflexes (especially gag, cough and corneal reflexes), but fell short of meeting the criteria for brain death declaration.

Hence, the most plausible explanation for lack of PLR in 10 (40%) of the critically ill neurological injury patients is underlying significant neurological lesion.

5. CONCLUSION

Our study makes a strong point for the clinical utility of 134apillary response to light after pharmacological neuromuscular blockade, especially in patients without neurological disease. In critically ill patients with serious brain insult, the lack of PLR is some patients probably can be attributed to the impairment of 134apillary light reflex mechanism from underlying significant brain lesion rather than the use of paralytic. Hence, the importance of evaluating 134apillary response in patients after use of paralytics stands tall and should be sought in every case.

6. LIMITATIONS

The sample size was modest. Patients were not randomized to different paralytic agents as Rocuronium was the only agent used, and

physicians were not blinded to medication used. Succinylcholine is not used frequently in the institute of this study for RSI as there is potential risk of raised intracranial pressure in patients with neurological diseases like in intracerebral hemorrhage. We wanted to maintain homogeneity of paralytic agent in our study with the use of Rocuronium in both case and reference groups.

Our study included acutely ill patients presenting in ED or ICU, posing significant time and logistic constraints in carrying out the protocol. There was drop of modest number of patients not meeting eligibility criteria in this study due to absence of raters at the patient's bedside. The ideal would have been only 2 raters for all the patients, but we had 4 raters (2 neurosurgeons and 2 medical officer) due to logistic challenge in carrying out this study. Although the use of pupillometer would have improved our ability to measure pupillary size, the absence of this instrument and time constraint in critically ill patients precluded its use.

Replication of this study with larger sample size and various neuromuscular blockade agents may result in different interferences. We tried to do maximum justice to this study considering time and logistic constraints.

7. FUTURE DIRECTION

Our next endeavor will be to conduct pupillary response to light in critically ill neurological patients in ICU over a protracted period of time post-intubation using RSI.

The effects of possible confounding variables like opiates, benzodiazepines and atropine will be ascertained. Large sample size and omission of above mentioned confounding variables in ICU setting if possible will help in this regard.

We will also like to perform the same study in non-emergency setting in the operating theater for patients with neurological pathology undergoing elective surgery.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Institutional Review Board approval was obtained prior to this study.

ACKNOWLEDGEMENT

We express our heartfelt gratitude to the doctors and medical staff involved in this study, without which this study would not have been possible.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/58680>