

Article

The Variation of Muscle Relaxant According to the Circadian Rhythm in Emergency Abdominal Surgery

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Abstract: In the contemporary anesthesiology services, muscle relaxation plays an integral role in emergency abdominal surgery in order to facilitate the work of the surgeons. Circadian rhythms control the behavioral, mental and physical changes of humans on a 24-hour cycle. The term circadian is originated from the Latin word “circa diem” meaning “around a day.” They are regulated by the suprachiasmatic nucleus SCN in the hypothalamus which is the “master clock” of the brain and the body. A study was carried on 50 patients both male and female from eighteen to sixty years old undergoing emergency abdominal surgery. The level of muscle relaxation administered intravenously was monitored using a TOF Watch SX time 08:00 till 14:00 then from 15:00 -20:00. Two different muscle relaxants were used notably “atracurium benzilate and rocuronium bromide” each at a dose of 0.4 mg/kg and 0.5 mg/kg respectively. The time of action for endotracheal intubation, duration and extubation was recorded. As a result, it was demonstrated that there was a significant shorter time of action and shorter duration in surgeries taking place from 15:00 pm-20:00 as compared to 08:00 -14:00 with both relaxants. To conclude, according to the circadian rhythm, effects of muscle relaxants in the evening relatively differed from the morning by having a shorter duration bringing to the fact that the cholinergic system had a role to play.

Keywords: Muscle relaxant, Neuro-Muscular block, Emergency abdominal surgery, Circadian time, Residual Neuro-Muscular block.

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1. Introduction

Various studies have proven that muscle relaxants facilitate not only the work of the surgeons but also that of the anesthesiologists. They ease intubation, avoid vocal injury and involuntary muscle reflexes during surgery. With the evolution of time the method of accelerometry permitted anesthesiologists to understand their action and effect on human and its elimination. However, many cases of residual neuromuscular block had been reported with and without the use of antidotes notably: “proserine or sugammadex” for their reversal [19].

Additionally, some cases of allergic reactions were being identified with the use of muscle relaxants during surgery leading to anaphylactic shock [8]. An exactly adequate dosage shall be administered, whether it is short acting, intermediate or long acting, the anesthesiologists should take extra care in administering muscle relaxants. The main challenge now is to prevent residual



NMB [12,13,14], stop losing time on extubation, amplify the methods in NMB monitoring world-wide.

Since many unwanted cases in surgery due to residual NMB are present, a TOF watch and a BIS monitor is highly recommended in all anesthesiological care centers for NMB monitoring before, intra and post- surgery. Intrinsically, the novelty of the study carried out denoted that time plays a key role on muscle relaxants. As the needle of the clock ticks evening time their duration is relatively shorter as compared to daylight [18] together with their frequency of elimination.

The circadian rhythm in our contemporary world plays a grand role in the process of a surgery where muscle relaxant is accountable. The usage of an appropriate dose, proper NMB monitoring in reliance to the circadian time decidedly is prioritized for zero residual NMB promoting quick recovery of the patient.

2. Patients and Methods

2.1. Materials of study:

The study consisted of 50 patients undergoing emergency abdominal surgery under combined endotracheal anesthesia using the following medications intravenously: phentanyl (30 mkg/ml), propofol (200 mg), sevoran, either rocuronium bromide (0.5 mg/kg) or atracurium benzilate (0.4 mg/kg). The apparatus used for mechanical ventilation was drager fabius. A protocol of clinical research together with the protocol of anesthesia and the pre-anesthesiological interrogation protocol were utilized. The ecg of the patients was taken before start of the surgery. For monitoring of the depth of muscle relaxant a Tof Watch Sx was used. Results were recorded on Microsoft excel and further graphs, tables were designed according to the Tof results obtained.

2.2. Methods to implement:

The effect of non-depolarizing muscle relaxants including (aminosteroid and benzylisoquinoline composition) was determined on neuromuscular conduction throughout emergency abdominal surgeries by using TOF Watch Sx in accordance to daytime 08:00-14:00 and evening time at 15:00-20:00. "Rocuronium bromide" and "atracurium benzilate" were administered intravenously in emergency abdominal surgery according to the following criteria: TOF 0, TOF 25 %, TOF 75 % and TOF 90 %. After administration of the 1st dose statistics were compiled on the result obtained. Two different muscle relaxants were used in to see how they react in different medical cases during emergency abdominal surgeries such as: laparoscopic appendectomy/cholecystectomy, hernia removal, relaparotomy sanitation and drainage of the abdominal cavity, dissection of intestinal adhesions, pancreatotomy. The blood pressure, the heart rate, the pulse -5 min after induction and after intubation, using capnometry, the ventilation parameters as follows :- PEEP, Tidal volume, PaCO₂, Ti:Te, FiO₂, sevoran and O₂) were monitored. An enquiry was conducted on the patients stating whether they took any medication in the anamnesis that can affect neuromuscular block. A query was being formulated on interrogation to the patients including the following: 1. They had a normal sleep or not- they slept normally 2. They did night shifts at work ?- none of them did 3. They did fly during the past few days - none of them flew anywhere recently [6,15].

2.3. Inclusion Criteria

- Adult male and female patients aged 18 to 60[21]
- Planned for a patient surgical intervention of medium duration (30–120 min)
- The severity of the condition before surgery according to the ASA classification (American Society of Anesthesiologists) - ASA Class I-III
- Patients with body mass index 18<BMI<30 kg/m²; Patients who have agreed to participate in the study, have read the Patient Information Sheet and signed the Informed Consent of the Patient, and are willing to cooperate in the course of the Study [21].
- Patients who are scheduled to undergo surgery using total intravenous anesthesia or combined endotracheal anesthesia (propofol, fentanyl, thiopental, midazolam, etc.) with an estimated duration of surgery of 30–120 minutes.

2.4. Exclusion Criteria

- Patients with significant disorders of neuromuscular conduction, neuromuscular diseases (including myasthenia gravis, Eaton-Lambert syndrome, a history of poliomyelitis, etc.) [22,23].
- Use in the perioperative period of drugs related to prohibited therapy in the study.
- Patients who have contraindications to the use of the TOF Watch device



(including Pacemaker, etc.);

- Acute infectious diseases.
- Patients with II-IV-degree burns.
- Patients with a history of hypersensitivity to drugs of the class used (pancuronium bromide, vecuronium bromide, atracurium benzilate, rocuronium bromide etc.)
- Patients with burdened allergic history (serious systemic manifestations of allergic reactions in history);
- Patients who participated in other clinical studies within the last 6 months. or currently participating in other clinical trials.
- Any other disease or condition that, in the opinion of the investigator, may confound the results of the study and limit the patient's participation in the study ASA IV.

A study was being carried out in the State Budgetary Healthcare Institution of the City of Moscow "City Clinical Hospital named after V.V. Vinogradov of the Moscow Healthcare Department"; (City Clinical Hospital No.64 of Moscow Department of Healthcare) situated in Moscow, Russia from the beginning of January 2023 to the end of February 2023 on 50 patients of the age of eighteen to sixty undergoing emergency abdominal surgery. They were classified into two groups; group 1 surgery which starts from 08:00 am till 14:00 pm then group 2 surgery which starts from 15:00 to 20:00. The TOF-reading demonstrates 4 phases or levels of muscular blockade:

1. Complete blockade
2. Deep blockade
3. Moderate blockade
4. Phase of recovery of neuromuscular block

Complete neuro muscular block happens after intravenous administration of muscle relaxant on intubation of the trachea, the rapidity of action and duration are related to the relaxant used [3]. This phase is known as TOF 0 period complete muscle paralysis where there is no result neither on TOF nor on post tetanic stimulation at PTC=0 according to the authors Wilson R.S, Savaresi J.J, Kitz R.J 1975, Brand J.B, Cullen D.J 1977; Deep blockade is characterized by absence of answers on the muscle tone by one stimulation and by the TOF regime as compared to complete blockade in which pops up answers at the post tetanic stimulation (moderate phase).

All patients were under combined endotracheal anesthesia with the administration of propofol and phentanyl together with sevoflurane and oxygen (MAC >1.0) supporting the anesthesia. Clinical monitoring was carried out using the international standards starting from the admission to the operation theatre till the implementation of anesthesia. Neuromuscular function was being measured each 15 seconds interval with the help of accelerometry all during the whole anesthesia with the help of the 4-x finger stimulation using the TOF Watch SX. The primary change of outcome at T1 was the time in minutes from the administration of the induction dose (0.5mg/kg) of rocuronium bromide or 0.4mg/kg atracurium benzilate.

3. Results

3.1. Variation of muscle relaxants morning and evening

(Table 1) illustrates the variation of the time in seconds and in minutes once a first intubating dose of rocuronium bromide 0.5mg/kg and atracurium benzilate 0.4mg/kg were injected intravenously. The time of action in seconds at TOF 0 of both the non-depolarizing muscle relaxants from 15:00-20:00 were shorter as compared to 08:00-14:00. A standard dose of 0.6mg/kg rocuronium bromide normally took 60 seconds to act but in the study a dose of 0.5mg/kg was given which took a bit longer and the surgeries were mostly emergency massive open abdominal ones which could be another potential factor for the lag of muscle relaxant in action per seconds. A standard dose of atracurium benzilate ranges from 0.5-0.6mg/kg took 90seconds to act normally but a dose of 0.4mg/kg was used which also caused a little delay in the action time. Atracurium Benzilate duration basically is 15 to 35minutes however for emergency patients its duration was up to 87.4mins and 75.5mins.

4. Discussion

It was supported by Ismail Gogenur et al [1,9] that during laparoscopic cholecystectomy LC with evaluation to open massive abdominal surgery MAS together with the circadian activity parameters (IS, IV and AMP). Comparing MAS to LC, MAS metrics proved to be worse. The circadian activity was grossly altered demonstrating that MAS beared more drastic modifications. Circadian activity pattern measurements and postoperative subjective recovery metrics showed



strong correlation [20,21]. Melatonin plays an integral role in medicine and can be used as a supportive drug in the treatment of sleep disorders, CNS disorders, GIT and cardiovascular system [10] and many oncological diseases due to its anti-inflammatory effect on the body, anti-oxidative and anti-carcinogenic, regulating mitochondrial function even affecting homeostasis with substantially an affect in the normal circadian rhythm- the sleep/wake program supported by Alicja Baranovskaya et al [2,5,8,11,24].

Table 1. A first intubating dose using rocuronium bromide and atracurium benzilate from 08:00-14:00 and 15:00-20:00.

Muscle Relaxant and time Intubating Dose mg/kg	Rocuronium Bromide 08:00-14:00 n=11	Rocuronium Bromide 15:00-20:00 n=12	Atracurium Benzilate 08:00-14:00 n=14	Atracurium Benzilate 15:00-20:00 n=13
TOF 0/secs	193.5± 94.3	129.6± 54.9	303.9±153.8	273.5± 84.4
TOF 25%/mins	38.6 ±8.1	35.5±4.9	54±9.5	42.5 ±7.2
TOF 75%/mins	68.3± 16.8	54.8±10.8	73.8±10.8	63± 16.5
TOF 90%/mins	87.5± 21	75.8 ±10.7	87.4 ±14.4	75.5 ±16.5

Note: TOF - Train of Four; TOF 0- Complete M. R, TOF 25%- M.R starts to fade away TOF 75%- Average fading of M.R TOF 90%-Time of recovery from M.R (muscle relaxant)

Circadian rhythms are the typically 24-hour biological cycles that serve to get a living thing ready for everyday environmental changes. [24] They are regulated by the molecular clock, which in mammals is a transcriptional/ translational feedback process including the key clock genes *Bmal1*, *Clock*, *Per1/2*, and *Cry1/2*. Almost all an organism's cells include the molecular clock. While the suprachiasmatic nucleus' (SCN) central clock has received extensive research, little is known about the clocks in peripheral tissues like the heart and skeletal muscle. One of the major organs in the body, skeletal muscle makes up about 45% of body mass. More than 2300 genes, many of which were involved in myogenesis, transcription, and metabolism, are expressed in skeletal muscle in a circadian manner. Skeletal muscle's circadian rhythms can be influenced directly by the timing of activity and food as well as indirectly by light input to the SCN. The skeletal muscle molecular clock must not only be entrained to the environment but also in time with the rhythms of other tissues to function properly. The documented consequences on skeletal muscle when circadian rhythms were disturbed include fiber type changes, altered sarcomere structure, decreased mitochondrial respiration, and poorer muscle performance. Skeletal muscle certainly contributed to the negative impacts on metabolic health because it is an important metabolic tissue. These negative consequences including reduced glucose tolerance and insulin sensitivity. These findings suggested that skeletal muscle circadian rhythms are essential for the health of both the muscles and the systems. Further studies are required to understand how skeletal muscle's molecular clock functions, pinpoint the processes behind entrainment, and conduct a thorough analysis of circadian gene expression in skeletal muscle's heterogeneous tissue system supported by Harfmann BD, Schroder EA et al.

It was discovered that on mice and humans that the first exposure to light had a greater influence on circadian phase shifting than subsequent exposures. For flesh flies, mice, and people, phase response curves to light exposure intervals with a variety of durations were available as supported by the authors Beersma DG, Comas M et al [6]. The progression of phase across a long interval (hours) of light exposure was reconstructed for each of these 3 species by comparing the phase changes generated by pulses of different durations but beginning at the same circadian phase. According to the phase progression curves for flies, weak resetting resulted in the pacemaker stabilizing about InT18 (near subjective dusk) after enough light pulses. While delays could be as long as 18 h, the phase progression toward the end value never indicated advances longer than 7 h. It is possible to discern clearly between advances and delays in type-0 phase response curves by using the phase progression curve method. This split between delays and advances happened in *Sarcophaga* flesh flies when light exposure begins at InT0 (subjective midnight). Previous research in mice that showed phase shifts were more strongly produced at the start of a light pulse



than they were during subsequent light hours. Within one hour of exposure, the response had completely decreased. It is believed that response saturation, rather than mechanisms of light adaptation, was more responsible for the fluctuation. Response saturation, as opposed to light adaptation, was crucial to the circadian pacemaker's effective operation during natural entrainment. Phase progression curves with naturalistic light profiles could be a useful tool for comprehending pacemaker entrainment to natural light.

The circadian rhythms of salivary melatonin and cortisol were found to be disrupted in patients with allergic rhinitis. These results might also be contributive data to explain the pathogenesis of allergic rhinitis and they could be applicable as adjunctive therapeutic tools in the future and melatonin drugs might be an alternative in the therapy of resistant allergic rhinitis patients or allergic rhinitis patients who cannot use cortisol drugs. Patients with inflammatory illnesses of the upper airway tract, such as allergic rhinitis, rhinosinusitis, and nasal polyposis, might have sleep impairment. A disturbance was discovered in the levels of salivary cortisol and melatonin in those with allergic rhinitis. It's possible that allergic rhinitis-related sleep issues are what's causing the aberrant cortisol/melatonin ratio by Fidan P et al [8].

Chronic pain and sleep disruption are connected. Greater emotional distress, worse function, greater pain intensity, lower positive affect, and higher degrees of catastrophizing were all linked to more sleep disruption. According to cross-sectional mediation analyses, the significant direct effects of sleep disturbance on chronic pain intensity as well as the significant indirect effects of elevated emotional distress, lower positive affect, and greater catastrophizing associated with sleep disturbance both statistically contributed to the positive associations between sleep disturbance and chronic pain intensity. Similar to this, it was discovered that the associations between sleep disturbance and impaired function were statistically supported by both the significant direct effects of sleep disturbance on function as well as the elevated chronic pain intensity associated with these associations. Both direct and indirect pathways have shown a substantial relationship between chronic pain function and sleep disturbance. These findings were in line with a growing body of literature that discusses the potential importance of sleep disturbance in chronic pain sufferers and offered more evidence for including sleep disturbance in the diagnosis and treatment of chronic pain Burjes HJ, Burns JW et al [15, 16].

An emerging field of study known as chrono nutrition focuses on the close connection between endogenous circadian (24-hour) rhythms and metabolism. Circadian regulation of metabolic activity could be seen at all levels of an organism, including postprandial reactions and whole-organism physiology. Recent research has shown how circadian clocks regulated metabolism in important metabolic tissues as the liver, pancreas, white adipose, and skeletal muscle. One peripheral organ's tissue-specific clock disruption, for instance, could lead to obesity or interfered with the body's glucose balance. Insights into mechanistic processes gleaned from research on transgenic animals along with how these findings were being applied to the study of human genetics and physiology. The principles of chrono nutrition had already been shown to enhance human weight loss and were anticipated to improve both the general public's health and that of those suffering from metabolic disorders Johnston JD, Ordovás JM et al [21].

Numerous studies demonstrated the significance of circadian variation in the excretion of hormones, the sleep-wake cycle, the rhythm of the core body temperature, the tone of the autonomic nervous system, and the regularity of activity for both healthy and disease-causing processes Gögenur I [9]. The diurnal fluctuation in endogenous rhythms in connection to surgery is also receiving more study. The focus had been on the possibility that postoperative healing, morbidity, and mortality might be impacted by circadian variation in endogenous rhythms. Several research was carried out examining various endogenous rhythms and factors impacting these rhythms considering the paucity of studies that have examined these endogenous rhythms in connection to surgery. A series of research addressing various endogenous rhythms and factors impacting these rhythms. These different endogenous rhythms had been explored in relation to surgery. Additionally, it was analysed whether there was a relationship between postoperative circadian rhythm disruptions and recovery metrics and whether pharmacological administration of chronobiotics could hasten postoperative recovery. All the investigated endogenous rhythms showed irregular circadian cycles. The first night following both minor and major surgery, there was a delay in both the excretion of the melatonin metabolite (AMT6s) in urine and the endogenous rhythm of plasma melatonin. The length of the surgery was linked to this recovery time following major surgery. The first night after major surgery, the amplitude of the melatonin rhythm remained unchanged, but it grew the following night. The first night after minimally invasive surgery, the amplitude in AMT6s was decreased. Both major and small surgery resulted in a disruption of the rhythm of the core body temperature. After major surgery, the sleep-wake cycle changed, with REM-sleep lasting noticeably longer throughout the day and at night than it did before. After major surgery, the autonomic nervous system's balance was also altered, leading to a markedly higher number of myocardial ischemia events at night. Both mild and major surgery affected the circadian activity pattern. After major surgery, the amount of AMT6s excreted during the daytime rose on the fourth



postoperative day. The total amount of AMT6s excreted in urine related to sleep efficiency and wake time after sleep initiation, but not with the occurrence of postoperative cognitive dysfunction. After a laparoscopic cholecystectomy, it was demonstrated that the effects of melatonin replacement in patients who experienced less pain than the median level for three days. Systematically it was demonstrated that circadian disruptions are present in the release of hormones, the sleep-wake cycle, the rhythm of core body temperature, the tone of the autonomic nervous system, cardiac ischaemia, and the rhythm of activity after surgery. Circadian rhythm characteristics and indicators of the effectiveness of surgical sleep and recovery are correlated. Based on the current data, oral melatonin therapy during the first three nights following surgery cannot yet be universally advised for enhancement of sleep quality or other recovery characteristics. Future studies must look into whether it was warranted in subgroups or whether different perioperative treatment methods were utilized.

Moreover, the effect of muscle relaxants on emergency abdominal surgery patients with relation to the circadian rhythm proving that their frequency of elimination and duration evening time was lesser than during the morning indicating that a further approach on the assessment of melatonin release intra and post abdominal surgery from 18:00 to 24hr should be closely evaluated together with muscle relaxants. The use of atracurium benzilate is mostly effective in emergency abdominal surgery because by the mechanism of Hoffman it does not depend on whether the liver or the kidneys to get eliminated by the body and it can be alternative to rocuronium bromide which mechanism of elimination is through bile from the liver and urine by the kidneys post abdominal surgery for patients without regurgitation for the betterment of the temp of homeostasis in relation to any noticeable affect of the circadian rhythm on critically ill patients transported from surgery theatre to ICU on pro longed mechanical ventilation.

5. Conclusions

1. At TOF 75% using rocuronium bromide in the morning from 08:00am to 14:00pm a difference of 14mins was recorded as compared to the time interval of 15:00pm to 20:00pm for a first intubating dose of 0.4mg/kg.
2. At TOF 75% using atracurium benzilate in the morning from 08:00 to 14:00 a difference of 11mins was recorded as compared to the time interval of 14:00 to 20:00 for a first intubating dose of 0.4mg/kg.
3. It is clarified that the non-depolarizing muscle relaxants notably rocuronium bromide and atracurium benzilate in the evening time tend to be lesser in duration as compared to morning time under combined endotracheal anesthesia for emergency abdominal surgeries.
4. In emergency abdominal surgery patients the time of action of both atracurium benzilate with a difference of TOF 0 at 30.4 seconds and rocuronium bromide 63.9 seconds are higher than expected morning time from 08:00-14:00 and evening time from 15:00-20:00.
5. Circadian hours can indirectly react on the metabolism, medicines, neuro muscular function and on the expression of receptors, a big amount of rocuronium bromide (75%) absorbed by the liver and excreted without a change in bile and the rest is excreted through urine or turning into active metabolites.
6. Experimentally it can be that there is a circadian modulation of the hepatic circulation. It was demonstrated that melatonin a hormone secreted by the pineal gland responding to darkness is related to the regulation of circadian rhythms. The circadian clock functions by a 24hour rhythm that takes longer than 24 hours but resets every day by the sun's light/dark cycle [7]. By taking melatonin supplements can also shift the timing of the body's clock. Melatonin acts on the cholinergic system and can relatively be a matter of concern.
7. A severe anesthesiological protocol was maintained with high standards of control of temperature (especially the drugs which act on the neuro-muscular block), dosage and physiological monitoring [2].
8. We used only combined endotracheal anesthesia protocol together with sevoran and regardless of the fact that sevoran increases the duration of anesthesia.
9. It was also proven that propofol acts on the circadian hours and itself can be the reason of its changes. We demonstrated the clinical effect of evening hours in the duration of neuromuscular block of rocuronium bromide and atracurium benzilate.
10. Anesthesiologists must expect that the duration of muscle relaxants (rocuronii and atracurii) is lesser at evening after 14:00 as compared to morning hours also it was supported by the author Abasova.I.S that the duration of neuromuscular block rocuronium bromide will be 1/3 lesser during evening time as compared to morning and nighttime.
11. Importantly the pharmacodynamics and pharmacokinetics of rocuronium benzilate and Atracurium benzilate must be considered while used during night hours.
12. It is to be considered that due to some troubles of recovery from rocuronium benzilate in many patients, sugammadex is preferably used for its reversal [4,13,14].



13. Moreover, during evening time, the evaluation of the dose of rocuronium benzilate and Atracurium benzilate should be considered for security reasons.

14. Rocuronium bromide should be given a minimal dose to critically ill patients for there is residual neuromuscular block many hours after surgery or rocuronium benzilate can be replaced by atracurium benzilate because the later does not depend on any liver or kidney failure and is metabolized by the Hoffman mechanism.

15. An adequate dose of muscle relaxant should always be estimated for it is the first step for a smooth anesthesia [15,16,17].

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