MEDICAL JOURNAL OF WESTERN INDIA

THE OFFICIAL PUBLICATION OF RESEARCH SOCIETY OF BJMC AND SGH, PUNE

WEBSITE: www.mjwi.org
ISSN NO.: 0972-9798
EISSN No.: 0972-9798

CLINICAL

Comparison of dose requirements and reversal characteristics of rocuronium when used as intermittent bolus and as an infusion- A prospective, double blind, randomised study

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ARTICLE INFO

Article history:
Date of Web Publication 13 Mar 2024

Date of Receipt: 13 Mar 2024
Date of Acceptance: 13 Mar 2024
Date of Publication: 01 Jan 1970
Article No: 203

ABSTRACT

Background- Rocuronium is an aminosteroid non-depolarising neuromuscular blocking drug used for general anesthesia with fast onset and intermediate duration of action. We studied dose requirement and reversal characteristics of rocuronium when used as intermittent bolus and as infusion. Objectives-The primary objective was to compare the haemodynamics, dose requirements and reversal characteristics of rocuronium when used as intermittent bolus and as an infusion.The secondary objective was to note side effectsiif any. Materials and methods- Total number of 60 patients undergoing general anesthesia were divided into two groups of 30 each randomly. Group B received intermittent bolus doses of rocuronium (0.15mg/kg) each and group I received initial bolus followed by continuous infusion of rocuronium as a muscle relaxant. Time of attainment of train of four(TOF) ratio of 90% and total dose requirements of rocuronium were studied in both the groups. Intraoperative heamodynamic parameters heart rate(HR), systlolic blood pressure(SBP) and diastolic blood pressure(DBP) were compared between two groups. Side effects if any were noted. Results-Time of attainment of TOF ratio of 90% was significantly lower in group B(31.50+2.93 min) as compared to group I (43.93+4.608min),P<0.01. Total dosage of rocuronium required was higher in group B (89.80+10.097mg) as compared to group I (83.43+7.96mg),P<0.01. Haemodynamic stability was better with infusion group(P<0.05). No side effects were noted in both the groups. Conclusion-In comparison with intermittent bolus dose, continuous infusion of rocuronium required lesser amount of total dose whereas recovery from neuromuscular blockade(TOF ratio) was delayed in continuous infusion group. Infusion group showed better haemodynamic

KEYWORDS

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Introduction-

Neuromuscular blocking drugs or skeletal muscle relaxants are firmly entrenched as integral part of present day anaesthetic practice. Anaesthesia providers practiced for nearly 100 years without these agents, but it would be difficult to provide the

same level of anaesthetic services today without their use.

Neuromuscular blockers should only be administered to patients to provide relaxation of muscles and not to abolish patient movement due to inadequate use of analgesics or depth of anaesthesia.[1]Awarene ss during surgery and intensive care units has been described and appropriate use of muscle relaxants is definitely a concern.[2,3]Neuromus cular blocking agents are used to facilitate the tracheal intubation as well as for maintenance of anaesthesia during surgery. To optimise the use of relaxants neuromuscular blockade should be monitored during surgery and depth of anaesthesia should be continuously assessed.

Rocuronium is a mono-quarternary steroidal non-depolarising muscle relaxant with a faster onset and intermediate duration of action. The onset time of rocuronium is significantly shorter with equivalent doses of other non-depolarising relaxants.[4] It can be administered as intermittent bolus injections or as continuous infusion. Infusion requirements of rocuronium ranges from 5 to 12 ug/kg/min.5

We conducted this study to evaluate time

to recovery of rocuronium, to compare dose requirements and reversal characteristics of rocuronium when used as intermittent bolus and as an infusion.

Materials and method-

It is a prospective, double blind, randomised, single centre study. After taking instituitional ethics committee approval and written informed consent, 60 patients were divided into two groups of 30 each randomly. Patients with 20 to 60 years of age, american society of anesthesia (ASA) physical status grade 1 and 2, anticipated surgery duration of two or more hours were included in the study. Exclusion criteria was pregnancy, cardiovascular, hepato-billiary or renal illness, and patients with known allergy. Patients were divided into two groups of 30 each by computer generated random number allocation. Group allocation was done by anaesthesiologist who was not the part of study design. Drugs were administered by the anaesthesiologist who was not the part of data collection and analysis. Group B received intermittent bolus doses of rocuronium (0.15mg/kg) each and group I received initial bolus followed by continuous infusion of rocuronium

as a muscle relaxant during the surgery.

In the operating room, intravenous (iv) canula was secured and standard monitors were placed. Monitoring included heart rate (HR), electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oxymetry (SpO2), end tidal carbon dioxide (ETCO2) . Neuromuscular blockade was assessed by measuring the contraction of adductor pollicis muscle by accelerography on stimulation of ulnar nerve. One arm was fixed, after cleansing of area over the course of ulnar nerve at the wrist, two surface electrodes were applied. Probe was placed on the distal part of the thumb, other fingers were fixed with a tape ensuring free movement of the thumb. Calibration of accelerometer was done using 0.2 ms supramaximal stimulus at 0.1 Hz. Ulnar nerve was stimulated with TOF stimulus (4 pulses of 0.2 ms duration each, frequency of 2 Hz, current intensity 40 mA). Skin temperature over adductor pollicis muscle was maintained more than 34 degree celsius by appropriate measures. Baseline (pre-induction) heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) of the patients were noted.

Patients were premedicated with glycopyrollate 0.2 mg iv, Ondansetron 0.08mg/kg iv and midazolam0.03 mg/kg iv. After preoxygenation with 100% oxygen for 3minutes, all patients were induced with thiopentone 5 mg/kg iv. and fentanyl 1ug/kg iv. As a part of standard anesthetic protocol all patients were receiving 50% nitrous oxide in oxygen gas mixture. After induction of anesthesia, Inj.rocuronium 0.6 mg/kg was given to facilatate tracheal intubation in both the groups.

After recording spontaneous recovery time from intubating dose to 95% baseline, group B received intermittent bolus doses of rocuronim of 0.15 mg/kg each to maintain two train of four(TOF) twitch response and group I patients were given continuous infusion of rocuronium which was titrated to maintain two TOF twitch response. Isoflurane 0.4-0.8% end tidal concentration with oxygen and nitrous oxide was used to maintain anesthesia.

Approximately thirty minutes before the end of the surgery, during stable anaesthetic conditions, at a first twitch recovery of 5% baseline, intermittent bolus doses and the infusion was stopped

and patients were allowed to spontaneously recover from the neuromuscular blockade. On appearance of all TOF twitch response and TOF ratio of 90% neuromuscular blockade was reversed with combination of glycopyrrolate 10ug/kg and neostigmine 0.05 mg/kg iv. Extubation was done on return of adequate tone, power and reflexes.

Time of attainment of 90% of TOF (T4/T1) ratio was defined as time from the beginning of bolus drug administration to spontaneous recovery of 90% of TOF ratio.

Total amount of rocuronium required during the surgery in both the groups were noted.. Side effects, if any were also noted .

Statistical analysis-

Preliminary sample size estimation showed that approximately 30 patients should be included in each group in order to ensure power of 80 %. Alpha error was assumed to be 0.05 (95 % confidence interval).

Patient characteristics were compared using 2 independent sample t test and chi square test. Intraoperative hemodynamic parameters, time of attainment of 90 % of TOF ratio and total dose of rocuronium required were compared using 2 independent sample t

test. P< 0.05 was considered significant, p > 0.05 not significant and p < 0.001 highly significant. Data analysis was done using SPSS (statistical package for social science) version 17.0 (SPSS inc., Chicago II,USA).

Results-

Demographic parameters age, sex and weight were comparable between both the groups and were not significant (Table1). Pre-operative hemodynamic parameters heart rate(HR), systolic blood pressure(SBP) and diastolic blood pressure(DBP) were similar in both the groups. But intraoperatively haemodynamic stability was significantly better in continuous infusion group (p<0.01).(Table 2).

Duration of surgery was comparable in both the groups (Table 3).

Time of attainment of 90% response to TOF was significantly prolonged in continuous infusion group (p<0.001) (Table 4).

Total dose of rocuronium required intra-operatively was significanty less in group I (p<0.01) (Table 5).

No side effects were noted in the study in any of the groups.

Discussion-

Monitoring of

neuromuscular function after the administration of muscle relaxants is vital to optimise the use of these agents and for the patient safety as well. In the operating room or intensive care unit depth of neuromuscular blockade is typically monitored by observing the response to stimulation of any superficially located neuromuscular unit. We observed response in adductor pollicis muscle to stimulation of ulnar nerve for the same purpose.

Neuromuscular blockers with intermediate duration of action have previously been shown to be suitable for administration by continuous infusion. Rocuronium is a non-depolarising muscle relaxant with intermediate duration of action and can be used in infusion. Previous pharmacokinetic studies after single bolus doses have shown the clearance and elimination half life of rocuronium to be 2.5-3.97 ml/kg/min and 104-131 min respectively.6

Agents used over longer periods by infusion may show a progressive decline in the drug infusion rate because of accumulation of drug in distributive compartments. The time of recovery of neuromuscular function were not unduly

prolonged after the infusions. The mean recovery time of 17 minutes after stopping the infusion was slighty less than that reported after single bolus doses of rocuronium.6

According to one study under isoflurane anesthesia the dose of rocuronium had to be decreased under stable anesthetic conditions. No dose adjustments was required under propofol anesthesia. This study also demonstrated that the potentiating effect of isoflurane is of pharmacodynamic origin and emphasizes the need for continuous monitoring of patient's clinical response.7

In our study both the groups were comparable with respect to demographic parameters and duration of surgery. We have considered patients undergoing major abdominal, pelvic and spinal surgeries done under general anesthesia.

The time of attainment of 90% of TOF ratio which is the major extubation criteria was significantly earlier with intermittent bolus doses. McCoy conducted a similar study to assess the pharmacokinetics of rocuronium after bolus and infusion under halothane anesthesia. The 90% of TOF was achieved in 31.4 minutes in bolus group

as compared to 36.4 minutes in infusion group.6

Inhalational agents, particularly isoflurane and enflurane, may enhance the neuromuscular blocking action of muscle relaxants. In the presence of steady state concentration of enflurane or isoflurane, it may be required to reduce the rate of infusion by 30 to 50% after 45 to 60 minutes of intubating dose. In our study isoflurane end tidal concentrations of 0.4 to 0.8% were used in both the groups to maintain anesthesia.9,11

In another study , isoflurane reduced the infusion requirement of rocuronium as compared to intravenous anaesthetic agents etomidate, fentanyl, midazolam, propofol and thiopentone.10 The interaction of rocuronium with isoflurane and with other five intravenous anesthetic agents was studied it was concluded that isoflurane decreases rocuronium infusion requirement by 35 to 40 %.

Recovery may be prolonged after infusions because of saturation of distributive compartments. In this situation distribution of blocker from plasma to peripheral

compartments contributes progressively less and less to reduction in plasma concentration.

Behaviour of rocuronium can be completely different in patients admitted to intensive care units(ICU).The pharmacokinetics of rocuronium was different in ICU patients than surgical patients. Volume of distribution was increased , plasma clearance was decreased and terminal half life was increased.8

Total dose of rocuronium required was significantly less in intermittent bolus group in our study. A study was conducted to predict the infusion rates of rocuronuim using the bolus test dose technique and it was found that the dose requirement of rocuronium infusion decreases with the increasing duration of infusion,from 60 mg/hr at the starting point to 15 mg/hr at the end.5

Upon reaching the desired level of neuromuscular block, the infusion of rocuronium must be individualised for each patient. In clinical trials, infusion rates have ranged from 4 to 16 ug/kg/min.

Intraoperative vitals were more stable in infusion group in our study. It has been found that the administration of relaxants by

continuous infusion provides for greater stability of drug concentrations and ensures greater consistency in degree of paralysis. When appropriately titrated to individual patient, infusion techniques have the potential to avoid periods of both inadequate and excessive drug effect.6

In comparison of intermittent bolus administration, the continuous infusion of intravenous anesthestic drugs provide greater control of anesthetic depth, thus ensuring better haemodynamic control, lower total drug doses and more rapid return to awake state.6

Liver disease alters the pharmacokinetics of rocuronium by increasing its volume of distribution. The longer elimination half-life might result in a longer duration of action of rocuronium in patients with liver disease, particularly after prolonged administration.12

In another study there was a significant difference between patients with and without renal failure in the rates of clearance 2.5 ±1.1ml kg-1 min-1 and 3.7± 1.4ml kg-1 min-1, respectively and the mean residence times 97.1± 48.7 min and 58.3± 9.6 min ($P < 0.05$). The differences in other kinetic parameters were not

significant. It shows that the effects of rocuronium may be prolonged in patients with renal disease, because of a decreased clearance of the drug.14

In a similar study on a small number of patients rocuronium appeared to be suitable for patients with chronic renal failure. There is no evidence of prolonged block even when the drug is given in repeated doses for maintenance.13

Neuromuscular blockade is greatly affected by use of volatile inhalational anaesthetic agents like isoflurane.9 We did not measure the depth of anaesthesia in our study and this can be considered as limitation of our study. However isoflurane was used in both the groups at a concentration of 0.4 to 0.8% end tidal, so it should not affect the results.

We have conducted our research on adult population Infants, pediatric and elderly may show different results due to altered total body water composition, volume of distribution and maturity of major organ systems.

Rocuronium is known to cause side effects like allergic reactions, pain at the site of injection, bronchospasm and arrhythmias. No such side effect was noted in any of the group.

Conclusion

Overall we found that when rocuronium is administerd as continuous infusion the total dose required is significantly less as compared to intermittent bolus doses and hence it is more cost effective. Also the degree of hemodynamic stability was better with infusion group. Time of 90% of TOF response was delayed with infusion group and therefore extubation and recovery may be delayed in infusion technique. No side effects were noted in our study.

[TABLE1]

SD – Standard deviation.

Table 1- Demographic profile of patients

[TABLE2]

SD- Standard deviation.

Table 2- Intraoperative haemodynamic parameters.

[TABLE3]

SD- Standard deviation

Table 3- Mean duration of surgery (minutes)

[TABLE4]

SD- Standard deviation.

Table 4- Mean time of attainment of 90% of Train of four(TOF) ratio

[TABLE5]

SD-Standard deviation.

Table 5 – Total dose requirement of rocuronium (mg)

[FIGURE1]

Figure 1-Total dose requirement of rocuronium(mg).

[FIGURE2]

Figure 2 - Duration of surgery (minutes)

Acknowledgement

Conflict of Interest

Financial Support and Sponsorship

Open Access Statement

How to cite the Article

http://mjwi.org/article-detail.php?artid=203

References

1. Cullen S. C., Larsen CPJ. Essentials of anesthetic practice. Chicago, year book, 1974. 2. On being aware. Br. J.Anaesth1979; 51:711-712. 3. Shovelton DS: Reflections on an intensive therapy unit. BMJ 1:728-737, 1979. 4. Wierda JM, Hommes FD, Nap HJ,Van dan Broek L. Time course of action and intubating conditions following vecuronium, rocuronium and mivacurium. Anaesthesia 1995; 50 :393-6. 5. Harrison MJ. Prediction of infusion rates of rocuronium using the bolus test dose technique. Anaesthesia 1997 Jan; 52(1):37-40. 6. E.P.McCoy, R.K. Mirakhur, V. R. Maddineni, J.M.K.H.Wierda and J.H.Proost : Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anesthesia. Br J Anaesth 1996; 76:29-23. 7. Alexandria dragne et al : Rocuronium pharmacokinetic-pharmacodynamic under stable propofol or isoflurane anesthesia. Can J Anesth 2002;49(4):353-360. 8. H.J.Sprarr, J.M.K.H.Wierda,J.H.Proost,C.Keller and K.S.Khuenl-brady. Pharmacokinetics and pharmacodynamics of rocuronium in intensive care patients. Br J Anaesth 1997;78:267-273. 9. Shanks C.A.,Fragen R.J.,Ling D.Continuous intravenous infusion of rocuronium(ORG 9426) in patients receiving balanced enflurane or isoflurane anesthesia. Anesthesiology1993;78:649-651. 10. Olkkola KT, Tammisto T. Quantifying the interaction of rocuronium (ORG 9426) with etomidate, fentanyl, midazolam, propofol, thiopentone and isoflurane using closed-loop feedback control of rocuronium infusion. Anesthesia and analgesia 1994;78:691-696. 11. Mayer M, Doenicke A, Hofmann A, Peter K. Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia. Br J Anaesth. 1992Nov; 69(5):511-2. 12. Magorian T, Wood P, Caldwell J, Fisher D, Segredo V, Szenohradszky J, SharmaM, Gruenke L, Miller R. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg. 1995Apr; 80(4):754-9. 13. Khuenl-Brady KS, Pomaroli A, Pühringer F, Mitterschiffthaler G, Koller J. The use of rocuronium (ORG 9426) in patients with chronic renal failure. Anaesthesia.1993 Oct; 48(10):873-5. 14. Cooper RA, Maddineni VR, Mirakhur RK, Wierda JM, Brady M, Fitzpatrick KT. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. Br J Anaesth. 1993 Aug; 71(2):222-6.