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Original Research

How Does Exponential Increase of Rocuronium Dose Effect the Train of Four Parameters in Rats-Reversed with Sugammadex? An Animal Model

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Abstract

Objective: Sugammadex is a gamma cyclodextrin structured agent used for reversing the effect of steroidal neuromuscular blocking agents. The first aim of this study is to evaluate the dose of rocuronium required to re-establish neuromusculer block (NMB) when its administered in 2 minutes after its reversal with sugammadex in rats. Also, to monitorize onset times and durations of NMB achieved by variable doses of rocuronium after reversal with sugammadex.

Methods: 35 Sprague Dawley rats were randomly divided into groups, including control and four experimental groups. The control group was designed to determine onset time and duration of NMB induced by 1.2 mg/kg rocuronium. In the control group no sugammadex applied. In the experimental groups, rocuronium (1.2 mg/kg) was reversed with sugammadex (4 mg/kg). Subsequently, experimental groups were administered various doses of rocuronium. Groups were named according to the rocuronium dose administered (Group 2.4, Group 3.6, Group 4.8 and Group 6.0). Rats in all groups were monitored with Train of Four.

Results: In group 2.4, rocuronium did not ensure neuromuscular blockade. In group 3.6, neuromuscular block was occured in only 3 rats. All rats in group 4.8 and group 6.0 achieved complete neuromuscular block. There was no statistically significant difference in the onset time of neuromuscular block in 4.8 and 6.0 groups ($p<0.05$). The mean duration of neuromuscular block in experimental groups was significantly shorter than the control group ($p<0.01$).

Conclusion: Sufficient muscle relaxation and intubation conditions could be achieved with 3,6 mg/kg, 4.8 mg/kg and 6.0 mg/kg doses of rocuronium as short as two minutes after sugammadex.

Keywords: Sugammadex, Rocuronium, Neuromuscular Block

Introduction:

Sugammadex is a gamma cyclodextrin structured agent used for reversing the effect of steroidal neuromuscular blocking (NMB) agents such as rocuronium and vecuronium via encapsulation [1]. In clinical practice sugammadex is widely used to reverse rocuronium induced neuromuscular block in post-operative care and emergency medicine.

Reoperation within the early postoperative period and re-intubation due to respiratory complications or allergic reactions are undesired situations which require neuromuscular blockade [2]. Theoretically, agents other than steroid structured NMB should be used to re-

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establish neuromuscular block after reversal with sugammadex [3]. However, rocuronium would be an alternative choice due to its rapid onset time and minimal hemodynamic changes even in high doses [4]. There are several case reports and studies on rocuronium being reused after reversal with sugammadex [5–8]. In these studies, there is no data on onset time or duration of neuromuscular block with rocuronium when its used to re-establish neuromuscular block after administration of sugammadex. The aim of this experimental animal study was to evaluate the dose of rocuronium required to re-establish NMB when its administered in 2 minutes after its reversal with sugammadex. Secondary end points of this study were to monitorize onset times and durations of NMB achieved by variable doses of rocuronium after reversal with sugammadex.

Material & Method:

Study subjects and study design

This experimental, randomized, controlled, blinded animal study was approved by the local animal studies ethical board. All invasive procedures, anesthesia, animal care etc were conducted in accordance with international guidelines on experimental animal studies [9].

Thirty-five female Sprague-Dawley rats weighing 180-300 gr were equally randomised into four experimental and one control group. Rats were kept in a temperature (22–24ºC) and humidity-controlled environment with free access to food and water. Sugammadex (Bridion; 200 mg/2 mL, Schering- Plough, Turkey) and rocuronium (Esmeron; 50 mg/5 ml Merck Sharp Dohme İlac, Turkey) were the agents used in this study.

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Anesthesia & procedural preparation: Following intraperitoneal ketamine administration (60 mg/kg) intravenous access was achieved using a 20-22G cannula in the tail lateral vein. Rats were secured on the dissection tray supinely and 1 L/m O2 was administered. Following 0.5cm incision on the midline of the neck, surgical dissectors were used to locate the trachea and place a 18G cannula as a tracheostomy (Picture 1a,1b). Thereafter, 1 ml of serum physiologique was administered to maintain hemodynamic stability due to possible blood loss.

Effect of NMB was monitored using Train of Four (TOF) (TOF-WATCH S, Oragon; Dublin, Ireland). The TOF stimulating part was placed using platinum needles neighbouring the sciatic nerve and its receiving part was placed in a pocket formed with surgical scissors between the gastrocnemius muscle and skin (Picture 1c). A stimulation with 2 Hz 0.2 ms was administered for 1.5 seconds every 15 seconds. Supramaximal current was determined to be T1/T4: 1.0 for the mentioned muscle groups.

Intravenous rocuronium (1.2 mg/kg) was administered to all rats with TOF measurements taken every 15 seconds. Rats were placed on 850 NEMI Scientific mechanical ventilators (Respiratuar Rate: 80-100, tidal volume 10 mL/kg) when their respiratory effort was lost. The control group was designed to determine onset time and duration of NMB induced by 1.2 mg/kg rocuronium. In the control group no sugammadex applied.

In all experimental groups, rocuronium (1,2 mg/kg) was applied, then time until TOF < 0.2 was recorded as ***t1***. Sugammadex at a dose of 4 mg/kg was applied when TOF < 0.2. After that, the time between administration of sugammadex and TOF > 0.9 was observed and recorded as ***t2***. Two minutes after TOF > 0.9, groups were administered various doses of

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rocuronium. Groups were named according to the rocuronium dose performed (Group 2.4, Group 3.6, Group 4.8 and Group 6.0). After second doses of rocuronium were applied in experimental groups, the time until TOF < 0.2 was defined as ***t3*.** The duration of action of rocuronium applied to the experimental groups for the second time and the duration of action of rocuronium applied to the control group was defined as *t4***.** All Steps of our study as a FLOW CHART has been demonstrated at Figure 1.

Statistical analysis was performed using IBM SPSS Statistics 16 (IBM SPSS, Turkey.) Kolmogorov-Smirnov test was used to determine normal distribution. One-way ANOVA with post hoc Tukey HSD was used to compare groups. Statistical significance was accepted as $p < 0.05$.

Results:

The average age of rats was 137,70±4,06 (133-145 days) and average weight was 187,24±15,43 gr (171-208). There was no difference between groups with regards to age, weight, basal body temperature or basal respiratory weight ($p>0.05$).

There was no statistically significant difference between groups with regards to ***t1*** and ***t2***. Neuromuscular blockade was achieved in no rats in Group 2.4 and only 3 rats in Group 3.6, whereas all rats in Group 4.8 and Group 6.0 achieved complete neuromuscular block. When Groups 3.6, 4.8 and 6.0 were compared according to ***t3***, no statistically significant difference was found. While a statistically significant difference was found between experimental and control groups for ***t4***, there was no difference in between experimental groups (Table 1).

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Relation between time and mean TOF values after the second dose of rocuronium following sugammadex administration are shown in Figure 2. Comparison of ***t4*** between groups is shown with box plot in Figure 3.

Discussion:

This experimental study has demonstrated that increasing dosages of rocuronium can be used for re-establishment of NMB after reversal of a rocuronium-induced NMB with sugammadex. However re-used rocuronium has a shorter duration of action when it's performed after sugammadex administration.

Rocuronium is the most commonly used steroid structured neuromuscular blocker agent. The use of steroidal neuromuscular agents for general anesthesia after reversal of neuromuscular blockade with sugammadex is controversial. If neuromuscular blockade is required after routine dosage of rocuronium (0.6 mg/kg) has been reversed by 4 mg/kg of sugammadex, 1.2 mg/kg of rocuronium or 0.6 mg/kg of rocuronium can be applied at the 5th minute or 4th hour respectively [3].

The timing and time to effect of recurrent doses of rocuronium is open to debate. In a case report, 0.6 mg/kg of rocuronium was reversed by 4 mg/kg of sugammadex. Emergency re-surgery was required 30 minutes later and adequate NMB was achieved at the 6th minute following 2 mg/kg of rocuronium [10]. In another case report, 0.6 mg/kg of rocuronium led to adequate NMB for intubation in 102 seconds, following the reversal of rocuronium with 2 mg/kg sugammadex 6 hours previously [8]. The authors reported that as the half life of sugammadex is 2 hours, a normal dose of rocuronium (0.6 mg/kg) would be adequate after 3

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half lives or more time had passed [8]. Case reports have reported varying times for administration of rocuronium following NMB reversal with sugammadex, with even more variation for dosage of 1.2 mg/kg and 3.4 mg/kg [2,11,12]. Although our study supports the hypotheses suggested by these case report examples, our goal is not only to determine the rocuronium dose after sugammadex in rats but also project the rocuronium doses in human.

In a study by De Boer et al [13], body distribution and drug pharmacodynamic and pharmacokinetics were used to determine the dosage of sugammadex required to reverse an initial dose of 0.6 mg/kg rocuronium and the required repeat dose of rocuronium to achieve NMB after sugammadex. The investigators determined that adequate conditions for intubation would be achieved with 1 mg/kg rocuronium for 2 mg/kg sugammadex, 1.5 mg/kg rocuronium for 4 mg/kg sugammadex and 2.25 mg/kg rocuronium for 8 mg/kg sugammadex respectfully. However, these findings do not correlate with previous case reports and the onset time of rocuronium was not specified in this dose determination study.

Cammu et al [5] reported a pilot study where the effect of 1.2 mg / kg of rocuronium following 4 mg / kg sugammadex was evaluated in 16 healthy volunteers. 1.2 mg / kg rocuronium was applied at differing times after reversal of NMB and their time to reach T1: 0% and TOF rate 0.9 were determined. They were grouped according to the time when rocuronium was performed after sugammadex (5 min n = 6, 5-25 mins n = 6 and after 25 min n = 5.) Average time to T1: 0% and time to TOF: 0.9 was 3.06m and 25.3 m for the 5m group, 3.09m and 24.8m for the 5-25m group and 1.73m and 38.2m for the over 25m group

respectively. In a later group, NMB commencement in volunteers was found to be significantly shorter. The study reported that the differing times of effect for rocuronium after sugammadex was not predictable in all patients. Therefore, the authors concluded that rocuronium usage after reversal with sugammadex was not a safe and feasible option [5].

To our knowledge there are no animal studies regarding the re-use of rocuronium after sugammadex, therefore, our study is the first in literature in this matter. When published case reports and volunteer-based studies are taken into consideration, literature generally reports re-use of rocuronium 5 minutes after sugammadex, more often than not 30 minutes after [8,11,12,14]. However, a recently published systematic review reported that allergic reactions and respiratory complications occur within the first 3 minutes after sugammadex administration [15]. Instead of evaluating re-dose of rocuronium after 5 minutes we therefore decided to evaluate the effect of various doses of rocuronium 2 minutes after reversal with sugammadex.

Some unforeseen complications have also been described after the widespread use of Sugammadex in anesthesia practice. Cases of acute coronary syndrome resulting from a strong allergic / immune reaction to any drug or product, also called Kounis syndrome, have been associated with the use of Sugammadex [21]. This newly described allergic condition has been described in many clinical presentations, from atropine resistant bradycardia to sudden cardiac arrest [21–24]. Both the aforementioned post-extubation respiratory complications and allergy-related coronary symptoms are conditions that develop in a short time and the findings of our

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study may guide clinicians in dealing with these clinical scenarios in case of re-intubation. We demonstrated that the time for reversal of neuromuscular blockade of rocuronium after sugammadex reversal of initial NMB was statistically shorter for the control group when compared to other groups. Clinicians should follow up closely for motor blockage in the event of such re-intubation.

In our study, the first dose of rocuronium was administered at 1.2 mg/kg. The suggested induction dose of rocuronium in humans is 0.6 mg/kg. However, due to faster metabolism this dose does not provide adequate neuromuscular blockade. Differing doses of rocuronium are used in rats while in most studies a high dose of 3.5 mg/kg [16,17] is used. It is reported that this dose corresponds to 0.6 mg/kg in humans. However, most studies have used lower doses of 1.2-1.5 mg/kg [18,19]. Our primary aim was not to determine the optimal human dosage but to evaluate differing doses according to total effect time and time to NMB. Therefore, we used the minimum accepted dosage of 1.2 mg/kg for rocuronium. We prevented mortality and complications by keeping experiment time and time on mechanical ventilation to a minimum. Intravenous sugammadex demonstrates linear pharmacokinetic properties over the dose range of 1-16 mg/kg. On the other hand when sugammadex is administered at high doses, the unbound sugammadex molecules will remain free, increasing the possibility of inducing toxic effects. Studies have shown that 1 mg of sugammadex is the equivalent of 4 mg in rats [19,20]. Therefore, we used 4 mg/kg of sugammadex so it corresponded to the minimum dosage in humans. To our knowledge there is no animal study, rat model or pilot study similar to ours in

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literature. There is also no study, similar to ours in which TOF usage in rats is demonstrated in detail.

In summary, the above-mentioned studies and case reports report that after reversal of neuromuscular blockade with sugammadex, high dosage (four times of normal) of rocuronium leads to neuromuscular blockade and an increase in rocuronium dosage after sugammadex lengthens the time for beginning of its effect. In our study we used 2-5 times more dosage to determine the effect of rocuronium after reversal with sugammadex. While 4-5 times higher dose led to neuromuscular blockade, there was no difference between the time of effect commencement between 4 or 5 times dosages.

Our study has some limitations. Due to technical reasons, we were unable to monitor blood gases and other physiological responses in rats. We had to ignore factors such as metabolic rate that would affect the effect time and metabolism of drugs. To prevent any negative effects of mechanical ventilation we kept rocuronium doses low. We were therefore unable to administer higher doses of rocuronium. Also, we did not perform any pathophysiologic evaluation of end organ effects of our experimental drugs.

To conclude, adequate neuromuscular blockade for intubation is possible when rocuronium is applied two minutes after sugammadex. However, the total dose of rocuronium, sugammadex and the time of requirement for intubation after sugammadex should all be kept in mind. A non-steroidal non depolarising neuromuscular blocker should be used in this case. Rocuronium can be used in 3-4 times of normal dose when other medications are not available. However, studies on the end organ effect of these dosages of rocuronium must be evaluated.

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Tables

Table 1. Comparison of t1, t2, t3, t4 times according to groups and number of curarized rats per group.

	Group 2.4	Group 3.6	Group 4.8	Group 6	Control Group	p
t 1 (sec)	77.14±21.38	74.3 ± 22.3	71.4 ± 25.4	77.1 ± 21.4	68.6 ± 18.6	0.935
t 2 (sec)	68.57±19.51	71.4 ± 25.4	88.6 ± 19.5	80.0 ± 28.3	-	0.395
t 3 (sec)	-	145.0 ±26.9	120.0 ± 23.1	100.0 ±24.6	-	0.080
Curarized Rats (n)	0/7	3/7	7/7	7/7	-	-
t 4 (sec)	-	310.0 ± 57.7	311.4 ± 33.8	360.0 ±86.4	514.3 ± 53.8	0.000

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Table 2. Comparison of ***t4*** between groups

	Control (n:7)	Group 3.6 (n:4)	Group 4.8 (n:7)	Group 6.0 (n:7)	p
Mean±SD	514,29±53,80	310,00±57,73	311,43±33,76	360,00±86,41	0,000*

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Figure Legends

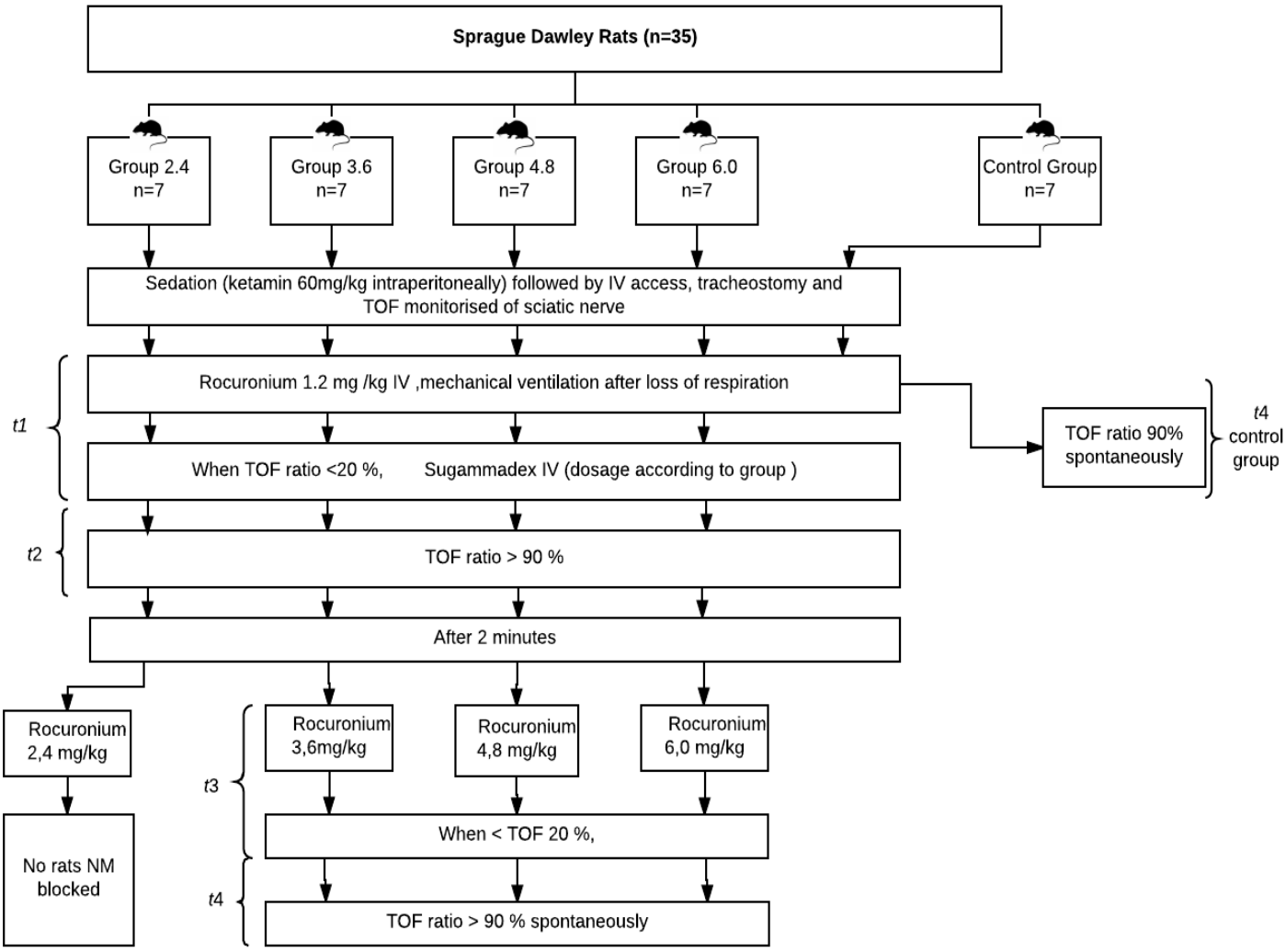

Figure 1. Steps our study as a flow chart

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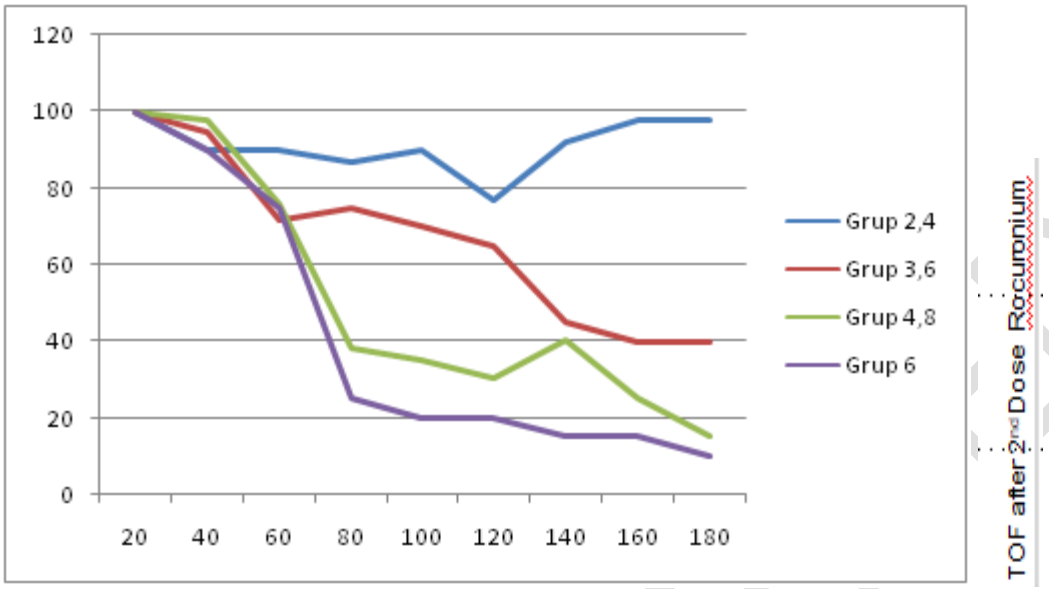

Figure 2. Relation between time and TOF values after second dose of rocuronium following sugammadex administration

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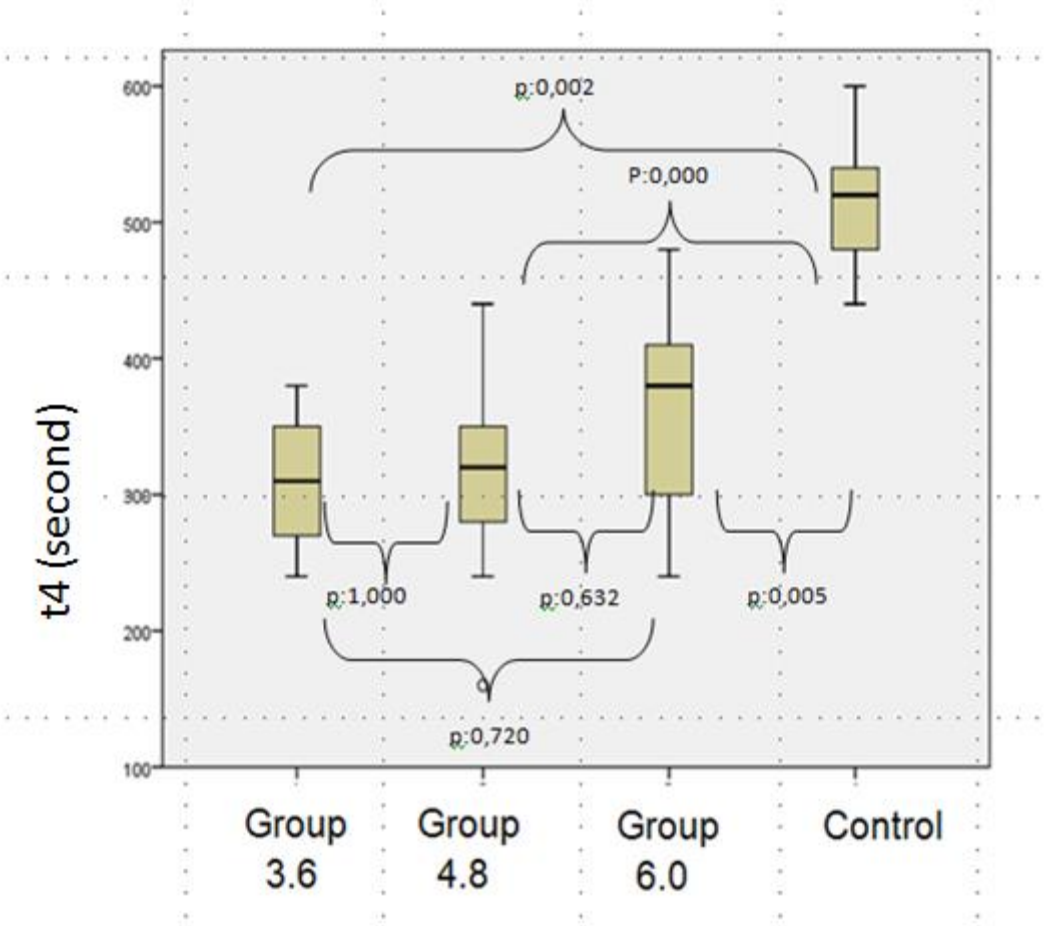

Figure 3. t4 as demonstrated as box plot.