A comparison of the effect of two doses of propofol with sodium thiopentone in the prevention of suxamethonium induced fasciculation and myalgia

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Abstract

Background: The use of suxamethonium commonly results in fasciculation and myalgia. This could be distressing to the patient. We compared the efficacy of high dose propofol, 3.5mg/kg with standard dose propofol, 2mg/kg and thiopentone sodium, 5mg/kg in reducing the suxamethonium induced fasciculation and myalgia.

Methods: A prospective double blind randomized study in 105 unpremedicated, ASA 1 or II patients, scheduled for elective general anaesthesia. They were randomized, and induced with propofol, 2mg/kg (Group P), thiopentone, 5mg/kg (Group STP) or high dose propofol, 3.5mg/kg (Group HP). Tracheal intubation was facilitated with IV suxamethonium (1mg/kg). The incidence and severity of fasciculation, 24 hours postoperative myalgia and creatine phosphokinase (CPK) levels were recorded.

Results The incidence ($p < 0.001$) and severity ($p = 0.034$) of fasciculation was significantly lower in Group HP than Groups P and STP. The incidence ($p < 0.001$), and severity ($p = 0.010$)of myalgia followed a similar trend. The mean 24hours postoperative CPK level was significantly lower in Group HP than Groups P and STP, $p < 0.001$.

Conclusion: It is concluded that high dose propofol is more efficient than standard dose propofol and thiopentone in minimizing suxamethonium-induced fasciculation and myalgia.

Key Words: suxamethonium, myalgia, fasciculation, creatinine kinase, propofol, sodium thiopentone

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Introduction

Suxamethonium, despite its quick and excellent skeletal muscles relaxation effects is associated with distressing fasciculation and postoperative myalgia.[1-3]The incidence of suxamethonium-induced myalgia in untreated patients is 5-83%,[4]and for fasciculation,it is 73-100%.[1-3]Suxamethonium induced myalgia is prominent in the muscles of the shoulder, neck, back, and abdomen,[2,5]and in ambulatory surgery.[1-2]Pre-treatment modalities such as non-depolarizing muscle relaxants, lignocaine, calcium gluconate, and diazepam have been reported to reduce suxamethonium-induced fasciculation and myalgia.[1,6]

A significant increase in creatine phosphokinase (CPK) level up to 5-7 times, with values of 110-3,000 IU/L have been reported after suxamethonium.[7-9]Higher doses of propofol and infusion during anaesthesia effectively prevented suxamethonium induced fasciculations, postoperative myalgia and CPK elevation than lower dose, and sodium thiopentone.[5-7] However, higher doses of propofol can lead to profound hypotension.[10] A decrease in systolic blood pressure (SBP) of 26-28%, diastolic blood pressure (19%), and mean arterial pressure (MAP) of 11%, without any change in stroke volume and cardiac output, were observed with propofol (2.0 mg/kg).[10]We compared the effect of high dose propofol with standard dose propofol, and sodium thiopentone in unpremedicated adult population on the incidence and severity of fasciculation, myalgia and CPK levels 24 hours following suxamethonium administration.

Materials and Methods

The study was a comparative double blind randomized control trial conducted at the Lagos University Teaching Hospital (LUTH) and the Federal Medical Centre (FMC), Ebute Metta, Lagos from June 2015 to May 2016. Approval for the study was obtained from the Ethical committees of LUTH and FMC, Ebuta Metta. A power analysis was conducted using proportions to determine an appropriate sample size; the incidence of postoperative myalgia,[6]and an assumption of 40% decrease in the incidence of myalgia with high dose propofol was used.[6] In order to achieve a power of 90% and $\alpha = 0.05$, a sample size of 35 per group was considered appropriate.[6]A total of 105, ASA I or II patients aged 16-60 years, scheduled for surgery under general anaesthesia with intubation facilitated with suxamethonium were recruited. ASA III and above, with severe cardiac, hepatic, or renal disorders, known allergy to study agents, individuals taking medications affecting CPK, neuromuscular function, or with neuromuscular disorders and myopathies were excluded. Also those

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requiring second dose suxamethonium, or with a history of masseter muscle spasm or malignant hyperthermia were excluded.

Anaesthetic Procedures

Preoperative review, routine investigations, and fasting were conducted according to hospital guidelines. No premedication was given. Baseline monitoring such as blood pressure, electrocardiograph, oxygen saturation (SpO_2), and temperature were commenced prior to induction of anaesthesia with a multi-parameter monitor [Datex Ohmeda Cardiocap 5, manufactured by General Electric Healthcare, Helskinki Finland]. All the patients were preloaded with intravenous (IV) 0.9% normal saline (10 ml/kg over 15-20 minutes) to minimize the effect of dehydration secondary to the fasting period. They were preoxygenated with oxygen (100%) for 3-5 minutes. Anaesthesia was induced slowly for 90 seconds with the injection of study drugs: Propofol was mixed with 1% plain lidocaine at 1mg per 1ml of propofol before administration.

Group I: Standard propofol group (P) patients received IV propofol (2mg/kg).

Group II: Sodium thiopentone group (STP) patients received IV Thiopentone (5mg/ kg).

Group III: High dose propofol group (HP) patients received IV propofol (3.5mg/kg).

All drugs were drawn and administered by research assistant 1 with at least two years of clinical experience. Complications during administration of induction drugs such as pain, apnoea, bronchospasm, laryngospasm were noted. Tracheal intubation was facilitated with IV Suxamethonium (1mg/kg). Ventilation was controlled manually during the apnoeic period using a face mask with Mapleson A breathing system until spontaneous respiration was re-established. The patient was not intubated during the observation of fasciculation unless there was an urgent need for it. The presence and the degree of fasciculation were assessed and graded visually by the primary investigator blinded to the study drugs used with a 4 point rating scale as described by Mingus et al.[11] I = no visible fasciculation; II = mild, fine fasciculations of the eyes, face, neck, or fingers without limb movement; III = moderate fasciculations occurring on more than two sides or obvious limb movement; and IV = vigorous or severe, sustained and widespread fasciculations requiring restraints.

Standard monitoring continued intraoperatively, blood pressure and HR were assessed 30 seconds post induction, on intubation and 2 minutes interval for the next 10 minutes post-intubation. Anaesthesia was conducted according to standard guidelines and patient needs. Postoperative pain was relieved with IV tramadol (50-100mg), and paracetamol (15mg/kg) as required. No intramuscular injection was administered during the perioperative period. Myalgia not related to surgery was graded with a 4 point rating scale as described by Harvey et al.[12] I. no myalgia = absence of muscle pain; II. mild = minor stiffness limited to one area of the body; III. moderate = muscle pain or stiffness noticed spontaneously by the patient, possibly requiring analgesic therapy but not causing disability; and IV. severe = pain at more than one site, causing disability as in turning of head and standing up. Patients observed to have moderate or severe myalgia not related to surgery with visual analogue scale (VAS = 5) 24 hours after induction had IV diclofenac (1mg/kg), and physiotherapy for severe discomfort.

Blood sample (4mls) was withdrawn for the estimation of CPK levels before and 24 hours after suxamethonium administration. Blood samples were immediately transported to the laboratory with ice packs in a thermocooler. It was centrifuged at 4°C (3000 g; 10 minutes), and the obtained plasma was stored at -20°C until analysis. On the day of analysis, the plasma and reagent were kept for 15-30 minutes to reach a temperature of 18°C-24°C. CPK assay was based on enzyme coupled reactions in which creatine phosphate and ADP is converted to creatine and ATP by CPK. The ATP is oxidized to NADPH (measured at 340 nm), which is proportionate to the CPK activity in the sample.

Case definitions

Hypotension was described as SBP <90 mmHg or MAP <60 mmHg or >20% reduction from baseline pressure. Hypotension was corrected with rapid administration of isoplasma or normal saline, with protracted hypotension IV ephedrine was administered in 3mg increments, and titrated to effect. Bradycardia was described as >20% reduction in HR from baseline or HR<60bpm, and arrhythmias was described as irregular rhythm. Bradycardia was managed with IV atropine (0.01 µg/kg), repeated doses were given when necessary up to 3mg. Hypoxia was described as SpO_2 <90% or desaturation to 92% for a period longer than 30 seconds. Hypoxia was treated with 100% oxygen, Apnoea was described as lack of respiratory effort for more than 30 seconds.

The primary outcome evaluated the effect of high dose propofol (3.5mg/kg) in comparison with standard dose sodium thiopentone (5mg/kg) and propofol (2mg/kg) on the incidence and severity of suxamethonium-induced fasciculation and myalgia, and CPK level 24 hours after induction.

The secondary outcome evaluated the changes in MAP, HR and complications after administration of the study medications; and the relationship between fasciculation and postoperative myalgia.

Data Analysis

The study results obtained were subjected to the

Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows computer program (SPSS Inc., Chicago, Illinois, USA).The continuous data were presented as mean and standard deviation, while categorical variables were presented as frequency and percentages. Comparison of the categorical data among the groups was performed using chi square test for incidence of fasciculation and postoperative myalgia. Kruskal-Wallis test was used to compare the severity of fasciculation and myalgia between the groups. CPK levels between groups and the intergroup difference was analysed with ANOVA test and Student t-test respectively. Pearson's correlation was used for relationship between fasciculation, myalgia, and CPK,p <0.05 was considered significant.

Results

The mean age, gender, weight, height, ASA status were comparable, p >0.05, (Table 1). A majority of patients had general surgery 52(49.5%) followed by gynaecology with 37(35.2%), and orthopaedics with 6(5.7%).

The incidence (p <0.001) and severity of fasciculation (p =0.034) was lower in Group HP than Group P, and Group STP, The incidence of and severity of myalgia followed a similar pattern, p <0.001 and p =0.010 respectively, (Table 2). The incidence of fasciculation was not related to the presence of postoperative myalgia in all the groups; the (Pearson's correlation (r) in Group P (r = 0.125) versus Group STP (r = 0.108) versus Group HP (r = -0.076), p = 0.56.

The 24 hours postoperative CPK values were higher than the baseline values in all the groups, p<0.001. The mean CPK was significantly lower in Group HP (100 ±46.42 IU/L) than Group STP (139.66 ±35.73 IU/L) and Group P (138.25 ±53.06 IU/L), p <0.001. Similarly, the percentage increase was lower in Group HP(26.63%) than Group STP (44.48%), and Group P(42.28%), p <0.001, (Table 3). There was no correlation between the presence of myalgia and elevation of CPK levels among the groups: Group P, r = -0.202, Group STP, r=0.213 and Group HP, r =0.081, p =0.37. Likewise, the severity of fasciculation was found not to influence the CPK levels in all the groups; r =0.24 in Group P, r =0.24 in Group STP, and r =0.14 in Group HP, (p =0.42).

There were 4(11.4%) cases of apnoea in the Group HP and none in Groups P and STP, p =0.564. In Group

Table1: Demographic Characteristics of Patients

Parameters	Group P Mean(SD) n = 35	Group STP Mean(SD) n = 35	Group HP Mean(SD) n = 35	P value
Age (years)	37.37 ±10.68	36.11 ±10.38	33.00 ±11.44	0.40
Weight (kg)	69.74 ±14.12	68.74 ±13.56	66.69 ±13.16	0.09
Height (m)	1.59 ± 0.79	1.59 ±0.64	1.59 ± 0.51	0.99
Gender ratio (M:F)	12:23	14:21	15:20	0.13
ASA classification ratio ASA I:II	24:11	26:9	24:11	0.49

Values are mean ±SD and p values.

Table 2: Incidence and Severity of Fasciculation and Myalgia

Parameter		Group P n =35	Group STP n = 35	Group HP n = 35	P value
Fasciculation Incidence		32(91.4)	34(97.1)	25(71.4)	< 0.001
	Severity				
	Nil	3(8.6)	1(2.9)	10(28.6)	
	Mild	5(14.5)	3(8.6)	10(28.6)	0.034Ŧ
	Moderate	25(71.4)	30(87.0)	15(43.5)	
	Severe	2(5.7)	1(2.9)	-	
Myalgia	Incidence	13(37.1)	17(48.6)	3(8.6)	< 0.001
	Severity				
	Nil	22(63.8)	18(52.2)	32(91.4)	
	Mild	8(23.2)	9(26.1)	2(5.7)	<0.010Ŧ
	Moderate	3(8.6)	5(14.5)	1(2.9)	
	Severe	2(5.7)	3(8.6)	-	

Values are proportions, p <0.05 is significant, Ŧ indicates Fischer Exact

Table 3: Changes in CPK levels

Group	Baseline CPK IU/L			24 CPK IU/L			% Increase CPK		
	Mean ±SD	P Values		Mean ±SD	P Values		%	P Value	
P	79.80±37.09	1.000†	0.806₸	138.25±53.06	< 0.001†	0.922₸	42.28	0.831₸	<0.001‡
STP	77.54±21.82		0.584‡	139.66±35.73		<0.001‡	44.48		
HP	73.99±39.76			100.85±46.42			26.63		

Values are mean ±SD and percent, p <0.05 is significant.
† indicate p value for all three groups; ₸ indicate p value for groups P and STP and † indicate p value for groups STP and HP. P value for groups P and HP at baseline, 24 hours and % increase were 0.493, 0.007 and <0.001 respectively.

HP, 10(28.6%) patients experienced pain on injection compared with Group P, 8(22.9%) and Group STP (0), p=1.000.

The mean heart rate and percentage change in mean heart rate showed no statistically significant difference among the three groups throughout the rest of the time interval.

Discussion

Our study demonstrated that high dose propofol effectively reduced the incidence and severity of suxamethonium induced fasciculation and myalgia compared with standard dose propofol and sodium thiopentone. The observed incidence of fasciculation in our study is within the reported range of 73-100% in untreated patients.[6] In contrast, lower incidences were reported by others; 48.5%, 76.8%, 78.8% respectively.[13] A similar observation was noted with propofol in repeated dose with total dose of 3mg/kg (33%) and total dose of 2mg/kg (23%), compared with single shot propofol 2mg/kg (90%).[14] The wide discrepancy in the incidence of fasciculation may be explained by the variation in use of premedication, electromyogram, dosage of suxamethonium, and techniques of administration of the induction agents, or observer difference.[1-3]

The incidence of postoperative myalgia in our study is within 1.5-92% in previous studies with or without pretreatment.[6,13] Myalgia was observed in 17(48.6%), 13(37.1%), and 3(8.6%) patients in groups STP, P and HP respectively in our study. A similar pattern was reported earlier, 60.7%, 59.3%, 30% respectively.[6] In contrast, the incidence was higher with 1% isoflurane (76%) and propofol 2mg/kg for induction plus 10 mg/kg/hr infusion (52%).[7] Likewise, in a meta-analysis, a higher incidence of myalgia was reported with propofol (49.2%) and thiopentone (65.4%), however, they were comparable.[1] The wide variance in incidence may be due to individual subjective perception of pain, difference in dosage and method of delivery of induction agents.[1,6,7] On the contrary, Maddineni et al.[14] observed that neither the induction agents nor the time between the induction agents, and suxamethonium administration had any significant influence on the incidence of myalgia.[14] Surprisingly, no premedication was given to any of their patients, though the administration of suxamethonium was either immediately or 2 minutes after the induction agent.[14]

We observed a significant increase in 24 hours postoperative CPK levels in all the groups. The lowest increase was noted with group HP. A similar observation was made by other researchers,[8,15] however, the magnitude of increase in CPK level was higher (225.7 IU/L,[8] and 392.1 IU/L[15]) than in our study (100-138 IU/L). This is surprising as they co-induced with remifentanil[8] and magnesium sulphate.[15] The variance in CPK surge after suxamethonium administration might be due to multiple confounding factors such as choice of volatile anaesthetic agent, degree of tissue damage, and time of assay of CPK. Such variables were controlled in our study, venous blood was withdrawn 24 hours after suxamethonium administration when serum CPK reaches its peak, and intramuscular injection was discontinued 48 hours prior to intervention.

In agreement with our study, there was no relationship between fasciculation and postoperative myalgia in previous studies.[2,11] Likewise, the severity of fasciculation and postoperative myalgia did not influence the CPK levels. A similar observation was made earlier following the administration of suxamethonium during surgery[9,15] and electroconvulsive therapy.[9] This may be because the mechanism of the myofibrillar disruption which results in increase in the level of CPK is different from the mechanism behind postoperative myalgia.[1,13] A significant increase in 24 hours CPK level observed by us, is linked to the peak time for CPK surge after skeletal muscle injury or damage.[6,13]

In group HP, 4(11.4%) patients developed transient apnoea while none in groups P and STP in our study. The apnoea improved with minimal respiratory support. In agreement, others have reported that propofol has a dose dependent respiratory depressant effect.[10] IV propofol (2.5mg/kg) resulted in apnoea in 5% of patients.[17] Whereas, when pentazocine was added to IV propofol

(2-2.5mg/kg), transient apnoea was observed in 80%.[18] The higher incidence of apnoea in the later study could be attributed to the synergistic effect of pentazocine on respiratory depression.[18]While we observed no apnoea with STP, apnoea in 25% of patients was reported following its administration.[17]The deliberate intention to inject STP at a very slow rate might be responsible for our observation. The occurrence of pain at injection of propofol (22.9-28.5%) is close to 25% reported in the region.[17-18]

Though a sharp reduction in SBP and HR after induction was observed in all groups, the values were comparable, this is in agreement, with previous studies.[6,13-14]We however, preempted the occurrence of hypotension by the administration of 10ml/kg of 0.9% normal saline to correct dehydration secondary to preoperative fasting, and we administered propofol slowly. The side effects of propofol has been reported to reduce by increasing the induction time.[19]While we reported no bradycardia, others observed bradycardia following sodium thiopentone[3,17] and propofol.[2,17-18]

A limitation to this study is the documentation of postoperative myalgia after 24 hours. Though, a similar study reported no difference in the incidence 24 hours versus 48 hours myalgia after surgery.[13]Nevertheless,it has been observed that 92% of patients complain of postoperative myalgia within 24 hours after surgery.[2] Therefore, it is assumed that our methodology would have captured most cases of severe postoperative myalgia. However, optimal intraoperative and postoperative analgesia may influence the occurrence of postoperative myalgia. In addition, the use of clinical judgment in the assessment of fasciculation is a limitation for objective assessment. A more objective tool is the use of the electromyography, which was unavailable at the time of the study.

Conclusion

It is concluded that high dose propofol for the induction of anaesthesia significantly reduced the increase in serum CPK, and minimized the incidence and severity of fasciculation and myalgia following suxamethonium administration compared to standard dose propofol and thiopentone.

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