Original Research Article

The comparison of the combined effect of preoperative diclofenac and precurarisation with atracurium on succinylcholine induced myalgia in laparoscopic cholecystectomy: A double blinded randomised study

Amit Tirkey[1], Tushar Kumar[2*], Mukesh Kumar[3], Ekramul Haque[4], Ladhu Lakra[5], Usha Suwalka[6]

[1]Resident, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[2]Assistant Professor, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[3]Assistant Professor, Department of Anaesthesiology- Cardiac Anaesthesia, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[4]Associate Professor, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[5]Professor, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[6]Professor and Head, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

Received: 24-11-2021 / Revised: 11-12-2021 / Accepted: 08-01-2022

Abstract

Background and Aims: Succinylcholine is the only available depolarizing neuromuscular blocker which was widely used in induction of anaesthesia and it is the drug of choice for rapid-sequence induction of anaesthesia due to its rapid onset of effect and ultra-short duration of action owing to its rapid hydrolysis by acetyl-cholinesterase. Post-operative muscle pain (myalgia) and muscle stiffness are the most common side effects and observed most frequently on the first postoperative day in ambulatory surgery. The use of succinylcholine in induction of anaesthesia and intubation in routine cases has been discouraged because of such adverse effects, however because of its cost effectiveness and easy availability it is still used by some institutions routinely. The aim of this study was to study the efficacy of pre-operative diclofenac along with atracurium precurarization alleviating succinylcholine-induced myalgia. **Material and methods**: It is a double blind randomised comparative study carried our in a tertiary care hospital. Study sample was 60 and divided in two equal groups. All data entered in MS-Excel Sheet and Wilcoxon Signed Rank test was done for non-parametric data and one way ANOVA for parametric data. The normal distribution of study sample was tested by Shapiro Wilk test. **Result and Conclusion**: The incidence of fasciculation in the two groups were found to be significant with $p < 0.00001$. The results for incidence of myalgia in the two groups were as follows - p value at 24 hr was 0.00018 and at 48 hr was 0.0028 respectively. Creatine kinase levels at preoperative and 24 hr postoperative period were 49.47 ± 7.24 in group D , 53.30 ± 7.98 in group B and 87.38 ± 15.16 in group D , 188.41 ± 33.27 in group B respectively. Succinylcholine induced myalgia has a complex pathophysiology, however the pre-emptive use of diclofenac in combination with precurarization can alleviate the incidence and severity of succinylcholine induced myalgia. Therefore its use may be considered in routine cases for induction of anaesthesia for facilitating laryngoscopy and endotracheal intubation.

Keywords: Fasciculation, myalgia, neuromuscular depolarizing agents, laparoscopy, non steroidal anti inflammatory agents, creatine kinase.

Introduction

Succinylcholine is the only available depolarizing neuromuscular blocker which is widely used in induction of anaesthesia and it is the drug of choice for rapid-sequence induction of anaesthesia due to its rapid onset of effect and ultra-short duration of action owing to its rapid hydrolysis by acetyl-cholinesterase. Postoperative muscle pain (myalgia) and muscle stiffness are the most common side effects and observed most frequently on the first postoperative day in ambulatory surgery. The use of succinylcholine in induction of anaesthesia and intubation in routine cases is discouraged because of such adverse effects, however because of its cost effectiveness and easy availability it is still used by many institutions routinely.

Creatine kinase has been used to quantify such tissue damage in many such studies on post-operative myalgia.

*Correspondence
Dr. Tushar Kumar
Assistant Professor, Department of Anaesthesiology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
E-mail: dr.tushar.kumar@gmail.com

Fasciculation induced by depolarizing muscle relaxants is reflected in deranged biochemical parameters with raised serum creatine kinase concentration in many subjects after its administration[1]. It has been suggested that the underlying mechanism of muscle damage associated with administration of succinylcholine may involve calcium induced phospholipids degradation with release of damaging products of fatty acid metabolism[2].

The use of NSAID may interrupt this prostaglandin-mediated destructive cycle and provide a rationale for their use in preventing succinylcholine-induced myalgia.

Myalgia and tissue damage are separate components of a complex picture of succinylcholine-induced tissue damage. Thus the pre-emptive dose of diclofenac when used in combination with precurarization might be helpful in considerably reducing the incidence and severity of succinylcholine–induced myalgia. Therefore, in this study, we want to evaluate the efficacy of preoperative dose of diclofenac in combination with atracurium precurarization, in decreasing succinylcholine induced post-operative myalgia in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

Materials and methods

The study was reviewed by institutional ethics committee (No: 188 IEC RIMS dated 21.12.2019) and registered in the clinical trial registry of India (CTRI/2021/02/031590). Our study followed the CONSORT guidelines for research. It was a randomised controlled study with double blinding.

The aim of our research was to study the efficacy of pre-operative dose of diclofenac sodium in combination Atracurium precurarization in decreasing succinylcholine-induced myalgia. The secondary objectives of study was to establish the association of fasciculation with postoperative myalgia and to study the association of creatine kinase with succinylcholine - induced myalgia. Inclusion criteria comprised those patients who were planned to undergo laparoscopic cholecystectomy surgery, of age 20 – 50 years of either sex and belonged to ASA grade I. The exclusion criteria stated that those patient who have allergy to the drugs used in our study, pregnancy, any neuromuscular disorder and any grade of hepatic or renal disease will be excluded from the study. Any laparoscopic surgery converted to open surgery due to any reason will be excluded from our study. Allocation was done by using computer generated random number in sealed envelopes. Double blinding was done by blinding the patients and the observer who assessed patients for myalgia. Operational definitions are as follows:

1) ASA Physical Status Classification System was used to assess the patient preoperatively and only the patients belonging to ASA status type I were included.

2) Myalgia grading scale was used to grade myalgia as follows:- 0-Absence of muscle pain, 1- Stiffness limited to one area only, 2-Muscle pain or stiffness noticed spontaneously by patient, which may require analgesic therapy, 3-generalised, severe or incapacitating discomfort[3].

3) Fasciculation grading scale on a scale of 0-3, where 0 = absent, 1=slight eyelid and facial fluttering, 2=large muscle twitching, 3= major limb movement[4].

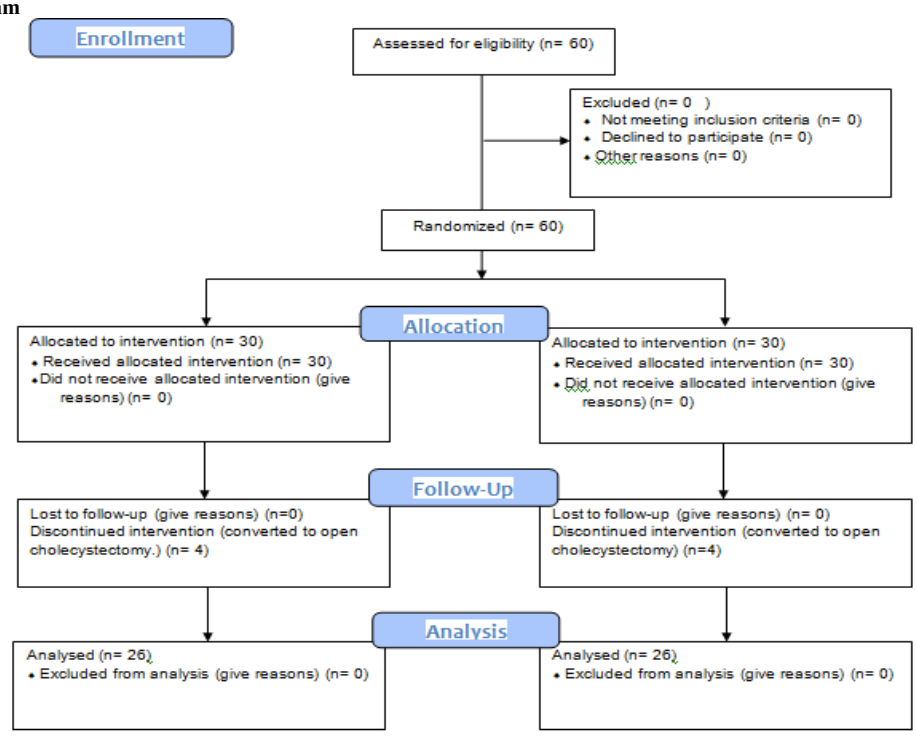
Patients were posted for laparoscopic surgeries pre anaesthetic checkup, confirming their ASA status as Type-I and taking informed and written consent from them, the patients were chosen randomly by allocation of computerized random numbers. Accordingly patients were allocated into 2 groups i.e B and D .All patients received Tab Ranitidine 150 mg and Tab Metoclopramide 10 mg the night before surgery. Group B received the placebo as Cap. B-complex (orally) 1 hour prior to induction of anaesthesia and Inj. Normal saline 0.9%(i.v) 3mins before administration of succinycholine and Group D received Cap. diclofenac sodium 100mg(orally) 1 hour before the induction of general anaesthesia and Inj Atracurium(i.v) 0.05 mg/kg 3 mins before administration of succinylcholine. All the patients were pre-medicated 30 mins before surgery with Inj Ranitidine 50 mg i.v and Inj. Metoclopramide 10mg i.v. Patients were pre-oxygenated with 100% O_2 for 3 minutes with normal tidal volume or 3 deep inspiration with 100% O_2 and then patient were induced with Propofol 2 mg/kg in slow incremental boluses followed by succinylcholine 1.5 mg/kg. Inj. Butorphanol 2 mg i.v was used for intraoperative analgesia. Maintenance of anaesthesia was done with N_2O+O_2+Isoflurane-1MAC.

The outcomes were listed as primary and secondary outcomes. Myalgia was assessed by an observer who was blinded to the administration of drugs . Grading of myalgia was done on a scale of 0 -3 according to myalgia grading scale, 24 hrs and 48 hrs after surgery. Patients with myalgia grading 1 to 3 were treated with injection paracetamol 20mg / kg iv, 2 to 4 times a day. Fasciculation after administration of succinycholine was assessed according to fasciculation grading scale on a scale of 0-3.Creatine kinase levels was checked at pre-induction and 24 hrs after the surgery respectively.

A pilot study on 11 patients revealed an incidence of 64% succinylcholine induced myalgia in our institution. Based on this assumption our sample size calculated as 55. Assuming the attrition rate of 10% our sample size for this study came up as 60.

All data entered in MS-Excel Sheet and One-sample Wilcoxon Signed Rank test was done for non-parametric data and one way ANOVA for parametric data. The power of study was kept at 80% with type 1 error of 5%. The confidence limit of 95% , p value of < 0.05 was considered significant. The normal distribution of study sample was tested by Shapiro Wilk test. Statistical analysis was done with Number Analytics LLC.

Consort flow diagram



Results

The study sample was normally distributed for weight with W = 0.96 and p = 0.206. Table 1 showed the demographic profile of patients.

Table : 1 Demographic Profile.

	Group D	Group B
Age	35.65 ± 7.77	39.65 ± 7.36
Sex(M:F)	10:16	16:10
Weight	59.03 ± 9.55	63.30 ± 11.9
Systolic BP	127.11 ± 9.29	126.42 ± 9.45

The incidence of fasciculation in the two groups were found to be significant with p < 0.00001.

Table 2: Incidence of Fasciculation.

Grade	Group D	Group B
0	22	1
1	3	7
2	1	9
3	0	9
P value	z = -4.2857. The p-value is < .00001. The result is significant at p < .05	

The results for incidence of myalgia in the two groups were significant at 24 hr and 48 hr post surgery. The p value at 24 hr was 0.00018 and at 48 hr was 0.0028 respectively as shown in table 3.

Table 3: Incidence of myalgia

Myalgia grading Scale	After 24 hours		After 48 hours	
	Group D	Group B	Group D	Group B
0	17	5	22	10
1	8	6	4	11
2	1	10	0	5
3	0	5	0	0
p value	.00018. p < .05.		.00288. p < .05.	

Table 4: Creatine Kinase level.

	Pre op		After 24 hours	
	Group D	Group B	Group D	Group B
CK level	49.47 ± 7.24	53.30 ± 7.98	87.38 ± 15.16	188.41 ± 33.27
p value	F-statistic value = 3.285 P-value = 0.0759		F-statistic value = 198.60 P-value = 0	

Table 4 shows level of creatine kinase Pre-operatively and at 24 hr post-surgery. The preoperative levels were comparable with p = 0.075 (> 0.05) but the post-operative levels indicate very significant rise in creatine kinase in control group.

Discussion

Succinylcholine is the most widely used depolarizing neuromuscular blocking agent because of its faster onset and ultrashort duration of action. The disadvantages are several, out of which muscle pain is a common complaint. Succinylcholine induced myalgia is often an ignored complication of general anaesthesia. In our study 15 patients complaint of myalgia in control group while only 1 patient had myalgia above grade 1. According to Wong S et al the incidence of succinylcholine induced myalgia ranges from 1.5 % to 89 % surgical patients[5]. Post succinylcholine pain and stiffness appearing on the day following surgery may last for 2-6 days and vary in intensity from mild malaise and tenderness to generalised and very severe pain[6]. Pain after 48 hours post surgery in group B was in 16 patients while in group D only 4 patients had pain (CL 95%; *p*= 0.00288) The gastric insufflation for laparoscopic surgery often lead to severe post-operative pain. There is increased intracellular calcium, increased

phospholipid disintegration and increased free radicals leading to increased membrane permeability[7]. Another theory suggested that due to fasciculation and contractions of muscle fibres there is shearing force at the onset of phase one block causing muscle damage resulting in pain[8]. There is no correlation between the elevation of creatine phosphokinase and the development of muscle pain but the increase in the serum potassium concentration is higher in patients who develop pain than in those who do not[9].

Analgesia used to blunt surgical pain also addresses myalgia due to succinylcholine. This may be the reason for paucity of myalgia cases after general anaesthesia. Use of atracurium in precurarizing dose reduces incidence of fasciculation and myalgia there by reducing post- operative muscle pain. Schrieber J U et al in a meta-analysis showed that non-depolarizing muscle relaxants, lidocaine, or magnesium may be used for the prevention of succinylcholine-induced fasciculation[10]. Our study revealed that fasciculations were more in group B as compared to group D (z = -4.28; *p = 0.00001*)

In our study the raised intraabdominal pressures might have been the cause of rise in creatine kinase. There is direct correlation between myalgia, fasciculation and creatine kinase level. There are studies which states that level of creatine kinase and pain are not related. We tested for the same and found that there is significant rise in fasciculation (p<0.00001), myalgia postoperatively (p at 24 hrs = 0.00018) and CK values at 24 hrs (p=0) in group B as compared to group D but on comparing the correlations between the two groups, results were not significant. The Fisher r-to-z transformation was used to compare fasciculation and creatine kinase levels between the two groups. The results yielded were z = 0.37 and p=0.71, which failed to establish any relation between fasciculation and creatine kinase. Similar results were obtained with myalgia and creatine kinase levels. The raised intra-abdominal pressures in our study sample may have raised creatine kinase levels enough not to establish any correlation between myalgia and creatine kinase level[11]. There is lot of biochemical activity occurring after vigorous muscle contractions which tends to increase creatine kinase and may cause muscle damage and pain[12]. Exercise related muscle damage is similar to succinylcholine induced fasciculation leading to myalgia. There may not be any actual muscle damage but muscle pain may be there. In the absence of any mechanical muscle damage, it remains a question as to whether raised CK after exercise does represent a degree of actual muscle damage or some form of disruption in energy control processes or some other molecular reaction mechanism[13].

Our hypothesis is that using diclofenac sodium and atracurium in precurarizing dose will yield less pain owing to decreased inflammation in muscles and lesser fasciculation, if any. Succinylcholine induced myalgia has been effectively managed by diclofenac sodium as shown by Rahimi M et al[14]. Fasciculation and myalgia in our study when compared in the two groups resulted in p value of 0.00001 and 0.00018 respectively. Due to precurarization and anti- inflammatory action of diclofenac, myalgia and fasciculation were blunted and resulted in lesser post-operative pain and discomfort. The rise in creatine kinase levels were also impeded in precurarization group than control group. The anti-inflammatory effect of diclofenac resisted the release of pro inflammatory cytokines and muscle damage[15]. Therefore in our study the effects of precurarization with atracurium and pre-emptive use of non-steroidal anti-inflammatory drug (NSAID) like diclofenac resulted in less post-operative muscular pain and enhanced patient comfort.

Conclusion

Succinylcholine induced myalgia is often overlooked by postoperative care givers. Muscle pain, apart from surgical pain causes psychological distress and discomfort. Sometimes increases length of hospital stay. The pathophysiology of succinylcholine induced myalgia is complex. However, pre-emptive use of diclofenac along with precurarization can alleviate the incidence and severity of succinylcholine-induced myalgia, so that use of succinylcholine can be considered in routine cases for induction of anaesthesia for facilitating laryngoscopy and endotracheal intubation.Various drugs are available for precurarization such as atracurium, vecuronium and rocuronium. NSAIDs such as diclofenac, being long acting competitive cyclo-oxygenase inhibitor, provides prolonged analgesic effect by inhibiting prostaglandin mediated pathogenesis of succinylcholine induced myalgia.

Conflict of Interest: Nil Source of support: Nil

References

1. Charak, d. S. & dhar, c. L. Suxamethonium-induced changes in serum creatine phosphokinase. British journal of anaesthesia **53**, (1981).
2. Mcloughlin, c., nesbitt, g. A. & howe, j. P. Suxamethonium induced myalgia and the effect of pre-operative administration of oral aspirin. Anaesthesia **43**, (1988).
3. Mencke, t., schreiber, j.-u., becker, c., bolte, m. & fuchs-buder, t. Pretreatment before succinylcholine for outpatient anaesthesia? Anaesthesia & analgesia **94**, (2002).
4. Naguib, m., farag, h. & magbagbeola, j. A. O. Effect of pre-treatment with lysine acetyl salicylate on suxamethonium-induced myalgia. British journal of anaesthesia **59**, (1987).
5. Wong, s. F. & chung, f. Succinylcholine-associated postoperative myalgia. Anaesthesia **55**, (2000).
6. Bryson, t. H. L. & ormston, t. O. G. Muscle pains following the use of suxamethonium in caesarean section. British journal of anaesthesia **34**, (1962).
7. Suarez-kurtz, g. & eastwood, a. B. Release of sarcoplasmic enzymes from frog skeletal muscle. American journal of physiology-cell physiology **241**, (1981).
8. Mizogami, m., fujibayashi, t. & goto, y. Succinylcholine-induced fasciculations in denevated rat muscles as measured using^{31}p-nmr spectroscopy. Acta anaesthesiologica scandinavica **42**, (1998).
9. Collier, c. B. Suxamethonium pains and early electrolyte changes. Anaesthesia **33**, (1978).
10. Schreiber, j.-u., lysakowski, c., fuchs-buder, t. & tramèr, m. R. Prevention of succinylcholine-induced fasciculation and myalgia. Anesthesiology **103**, (2005).
11. Cardia, g., centonze, a., cianci, v., malcangi, v. & brienza, n. Abdominal compartment syndrome: a situation thet needs to be better known. Chirurgia italiana **60**,.
12. Clarkson, p., byrnes, w., mccormick, k., turcotte, l. & white, j. Muscle soreness and serum creatine kinase activity following isometric, eccentric, and concentric exercise. International journal of sports medicine **07**, (1986).
13. Baird, m. F., graham, s. M., baker, j. S. & bickerstaff, g. F. Creatine-kinase- and exercise-related muscle damage implications for muscle performance and recovery. Journal of nutrition and metabolism **2012**, (2012).
14. Rahimi, m., makarem, j. & goharrizi, a. G. Succinylcholine-induced myalgia in obstetric patients scheduled for caesarean section--diclofenac vs placebo patches. Middle east journal of anaesthesiology **20**, (2009).
15. Nieman, d. C. Et al. Muscle damage is linked to cytokine changes following a 160-km race. Brain, behavior, and immunity **19**, (2005).