Effects of rocuronium pretreatment on muscle enzyme levels following succinylcholine

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Abstract: Succinylcholine revolutionized anaesthetic practice by providing intense neuromuscular blockade of very rapid onset and ultrashort duration, thereby greatly easing the maneuver of tracheal intubation. However the worth of succinylcholine is limited by the frequent occurrence of muscular side effects which manifest biochemically in the form of rise in serum creatine kinase (CK). The administration of small doses of nondepolarizing muscle relaxants before the administration of succinylcholine has been shown to decrease the incidence and severity of muscular side effects experienced by the patients. This study was aimed at evaluating the efficacy of technique in reducing the muscular side effects of succinylcholine, biochemically manifested as rise in CK. Sixty healthy adults were enrolled in the study who were scheduled for minor muscle cutting surgeries under general anaesthesia. They were assigned at random to two groups of thirty patients each. They randomly received succinylcholine for intubation and a precurarization dose of rocuronium followed by succinylcholine for intubation. Blood samples were drawn for estimation of serum creatinine kinase. There was a significantly raised CK in the succinylcholine group. In the precurarization group the rise in CK was prevented and the levels were significantly less as compared to the group which received succinylcholine alone. Present study concluded that precurarization with rocuronium was effective in reducing the succinylcholine-induced rise in creatinine kinase.

Keywords: Succinylcholine, rocuronium, creatinine kinase, precurarization.

INTRODUCTION

Succinylcholine is the most commonly used and a cost effective neuromuscular blocking agent available in the markets of Pakistan for endotracheal intubation. It has been in the core of anaesthetic practice for more than 60 years now and is usually preferred for the fear of prolonged or failed intubation (Mirsad *et al*., 2010). No other drug can compete in muscle relaxation, speed of onset and short duration of action and that is why despite its limitations and side effects, succinylcholine is still used for endotracheal intubation. However since its introduction into clinical practice it has been recognized that muscular side effects biochemically manifested in the form of rise in serum creatine kinase occurs frequently with its use (Wong and Chung, 2000). Non depolarizing agents avoid this problem, but none has the same pharmacokinetic profile as succinylcholine. Rocuronium and the newer rapacurium come nearer, but both have longer lasting effects than succinylcholine and so they too could not replace it. Several strategies have been advocated to decrease the incidence of this adverse effect, one of the most successful being the administration of small doses of nondepolarizing neuromuscular blocking agents before administration of succinylcholine (Abbas *et al*., 2009). The terms defasciculation and precurarization are used synonymously with the efforts to minimize the muscular complications of succinylcholine use (Cannon, 1994). Many factors influence the efficacy of pretreatment, including the choice of nondepolarizing agent, degree of prejunctional receptor block, interval between administration of pretreatment agent and succinylcholine and speed of onset of nondepolarizing agent (Erkola, 1988). Rocuronium provides good intubating conditions as it has more rapid onset of action compared with the established nondepolarizing agents. As the most favorable interval for pretreatment with pre-existing is approximately 3 minutes, this property of rocuronium may be pertinent to its use in prophylaxis of muscular side effects after succinylcholine pretreatment on frequency of post operative muscular effects (Motamed *et al*., 1997). Although this has been supported by a very few studies and most of the studies done so far have come up with mixed results. No such study has ever been conducted in Pakistan encompassing this parameter. Although studies have been conducted comparing the intubating conditions with succinylcholine and rocuronium or observing fasciculations and postoperative myalgia with succinylcholine, but no work has been conducted regarding the changes in the biochemical markers with the use of the two drugs.

MATERIAL AND METHODS

This study was carried out in the operation theatre of Combined Military Hospital, Rawalpindi after approval of the study project by ethical committee. Written informed

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consent was taken from all subjects undergoing elective minor muscle cutting surgeries. It was a prospective, single blinded and randomized study. It included 60 patients who were allocated randomly to one of the two groups. Patients in group "A" received succinylcholine and group “B” received precurarization dose of rocuronium followed by succinylcholine. There were 30 patients in each group. The two groups were comparable in respect to age, sex and weight. Patients of either sex aged from 18 to 65 years of ASA grade I and II were included in this study. Preoperative evaluation included detailed history, general physical, systemic and upper airway examination. Investigations were carried out to exclude liver disease, hepatitis B and C, renal disease and heart disease in study subjects. These all findings were recorded on a pre-clinical and clinical proforma. Routine monitoring was done after receiving the patient in theater. Standard anaesthesia technique was employed in all patients. Intravenous line was secured. Group "A" received succinylcholine 1 mg/kg body weight (Naguib *et al*., 2006). Group "B" received 0.1 mg/kg rocuronium followed by succinylcholine 1.5 mg/kg body weight for intubation (Bevan and Donati,1997). These drugs were given by an anaesthetist who was not included in rest of the study. Direct laryngoscopy was performed and the patients were intubated via oral route, 60 seconds after giving drugs for intubation. Anaesthesia was maintained with the maintenance doses of the volatile anaesthetic agent isoflurane and 60 percent nitrous oxide in oxygen. Venous blood samples of two millilitres (ml) was obtained before induction of anaesthesia at 0 hours for the measurement of serum CK. The second blood sample was drawn at 24 hours postoperatively after the induction time (Ozlu *et al*., 2002). The serum CK was estimated using ultraviolet (UV) -Kinetic method at AFIP (Faulker and Meites, 1982).

Data was analyzed using SPSS version 16. Descriptive statistics were used to describe the data. Mean and standard error of mean (S.E.M) were used to describe quantitative variables like age, weight and CK. Quantitative variables were compared through analysis of variance (ANOVA) between the groups. Paired sample t-test was used to compare initial and final values of CK within the groups. Chi-square test was used to compare qualitative variables between the groups (Abbas *et al*., 2009). *P* value <0.05 was considered as significant.

RESULTS

There was no significant difference in patient characteristics in the two groups and they were well matched for age, weight and sex. Each group had 30 patients (Group A: 17 males and 13 females and Group B: 16 males and 14 females). The mean age of Group A patients was 39.97±1.833 years (range 18-65 years) and of Group B was 36.63±1.791 (range 18- 65 years). At the start of the study (at 0 hours), in group A average serum CK level (±S.E.M) was 93.40±8.836 IU/L, in group B it was 78.40±6.669 IU/L. There was insignificant difference between the groups (P=0.340) (table 1). At 24 hours, average serum CK level in group A was 440.20±51.38 IU/L. In group A, the increase in serum CK level from the start of the study to 24 hours was highly significant ($p < 0.001$) (table 1). In group B average serum CK level at 24 hours was 108.73±7.149 IU/L. In group B, the increase in serum CK level from the start of the study to 24 hours was highly significant (P<0.001) (table 1). Average increase in serum CK level or difference of mean in group A was 346.80±50.24 IU/L and in group B it was 22.30± 3.903 IU/L (table 2). The change in serum CK level was significantly more in group A as compared to group B (P<0.001) (table 3).

Table 1: Initial and final levels of serum creatine kinase (CK) in group A and B

	Group A (n= 30)	Group B (n= 30)
At 0 hrs	93.40 ± 8.836IU/L	78.40 ± 6.669IU/L
After 24 hrs	440.20±1.38*IU/L	100.70±6.383*IU/L

P<0.05

Table 2: Comparison of change in serum creatine kinase (CK) level between the groups

Groups	Difference of Mean	S.E.M
Group A (n=30)	346.80	50.24
Group B (n=30)	22.30	3.903
p value	<0.001	

Group A vs Group B: *p* value *

Table 3: Comparison of serum creatine kinase (CK) between group A and group B

	Group A (n=30)	Group B (n=30)
At 0 hours	93.40±8.836^{NS}IU/L	78.40± 6.669^{NS}IU/L
After 24 hours	440.20±51.38*IU/L	100.70± 6.383*IU/L
Difference of Mean±S.E.M	+346.80±50.24	+22.30±3.903

^{NS}Not Significant *p*<0.05, S.E.M Standard Error of Mean
+An increase in the average after 24 hours

DISCUSSION

Securing the airway is of prime importance in patients at risk of aspiration of the gastric contents during general anaesthesia, such as having a full stomach, delayed gastric emptying times, hiatal hernia or incompetent lower oesophageal sphincter. Succinylcholine is the gold standard for this purpose. It is an ideal drug for short surgical procedures during the day care surgeries. It is

also the drug of choice in clinical situations in which rapid paralysis and airway control remains the main priority (Thapa and Brull, 2000). However some of its untoward effects limit its usefulness.

CK measurement in serum has remained the best overall marker for detection and monitoring of skeletal muscle diseases and damage (Simpson *et al*., 2002). Other enzyme markers for skeletal muscle injury: Aldolase, enolase, aspartate aminotransferase and lactate dehydrogenase isoenzyme are not as specific as CK (Simpson *et al*., 2002).

There is biochemical evidence of muscle damage with raised serum CK concentration in many subjects after the administration of succinylcholine (Fitzpatrick, 2008) and has proved to be the most important agent for the release of CK from muscles during anaesthesia (Innees and Stromme, 1973). This marked rise in serum CK is related to tissue trauma and injury occurring postoperatively with maximal level recorded at 24 hours after operation, followed by a decline towards normal in five days (Swell *et al*., 1971). Marked changes in serum CK occur after major muscle cutting surgeries indicating the extent of muscle damage but the same remains negligible after a minor surgery. So only those patients were included in our study who were undergoing minor muscle cutting surgeries so as to minimally affect the results and all the patients undergoing major muscle cutting surgeries were excluded (Yousef *et al*., 2006; Laurence, 2000). We studied CK level at 0 hours and thereafter at 24 hours postoperatively. We found that there was an overall rise in serum CK in all the three groups we compared. Average increase in serum CK level in group A was 346.80±50.24 IU/L. This highly significant rise was related to succinylcholine being given for intubation. Tammisto reported rise in CK in a group of ophthalmological patients after intermittent doses of succinylcholine chloride under halothane anaesthesia (Tammisto and Airaksinen, 1965). Similar observations were made in a study by Kudoh, where administration of succinylcholine caused a marked increase in serum CK concentrations in paediatric patients. However the clinical significance of this finding remained uncertain (Kudoh *et al*., 1997).

In our study the rise in serum CK level was statistically significant in group A as compared to group B. Although our study demonstrated an average increase in serum CK in the group B where patients were precurarized with rocuronium however this increase was within the normal range, signifying the effectiveness of precurarization with rocuronium. The rise in serum CK level was statistically insignificant between group A and group B. For the prevention of this adverse effect on muscles, different studies have been carried out. Ozlu established the efficacy of rocuronium pretreatment at 30 minutes, six hours and 24 hours in preventing the succinylcholine associated rise in muscle derived enzymes (Ozlu *et al*., 2002). Our results have evaluated rocuronium pretreatment in group B to be effective in preventing succinylcholine-induced rise in serum CK. In a study by Laurence, the use of alcuronium has been established for abolishing the rise in CK at 24 hours (Laurence, 1987). A year later Theroux evaluated mivacurium 0.03 mg/kg effective in reducing the increase in CK at 24 hours (Theroux, 2001). Our result compared well with the studies.

This study has statistically proven the effectiveness of precurarization with rocuronium in reducing the rise in CK which is the marker for muscular damage. In other words it is effective in preventing postoperative myalgia, the analgesic requirement associated with it and most importantly the distress of the patients (Abbas *et al*., 2009). The resulting early mobility decreases the chances of deep vein thrombosis and also promises earlier restoration of gastrointestinal functions.

This study substantiates the significance of establishing treatment regimens to decrease the adverse effects of succinylcholine. Effective side effect control practices such as precurarization technique shall surely encourage and therefore increase the use of such a cost effective drug. Despite few untoward effects, succinylcholine offers several unmatched advantages over the other neuromuscular blocking agents. The nondepolarizing neuromuscular blocker which has the onset of action closer to that of succinylcholine is rocuronium, but the drug is quite expensive and has a longer duration of action, making it unsuitable for endotracheal intubation in short surgical procedures.

Because of the implacable persistence of succinylcholine in our anaesthetic practice, new innovative research with this muscle relaxant should be encouraged to improve its side effect profile. The technique evaluated in this study is one such method which may be implemented, keeping in view the major benefits of succinylcholine over its contemporary drugs.

In conclusion, it is suggested that sincere efforts are required to find the efficacy of a technique which could significantly reduce the undesirable side effects of succinylcholine in order to limit the valuable hospital cost being spent on the health of the patients in our poor country. This study has statistically proven the effectiveness of precurarization with rocuronium in preventing succinylcholine induced rise in serum CK. Thus decreasing the postoperative analgesic requirement associated with it, and most importantly the distress of the patients. This shall encourage the early ambulation of patients after minor surgeries, significantly reducing the time during busy operating lists. The resulting early mobility decreases the chances of deep vein thrombosis

and also promises earlier restoration of gastrointestinal functions. This study was targeted at decreasing these side effects of succinylcholine by giving only one fifth of the dose of rocuronium. Rocuronium available in the market is very expensive as compared to succinylcholine. For using it as a pretreatment drug, patients will have to pay more. It would therefore be unfair to use the drug without documented evidence of the benefit of this technique. The implication of precurarization will decrease the side effects of succinylcholine effectively. The technique is cost effective as it cuts the cost of intubation on each patient to one fourth as compared to the newer nondepolarizing agents alone and reduced postoperative analgesic requirements resulting in decrease in burden on the hospitals.

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