VOLUME OF DISTRIBUTION OF ATRACURIUM IN DIFFERENT COHORTS: A COMPARATIVE STUDY
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ABSTRACT: BACKGROUND: Comparison of volume of distribution of Atracurium in peritonitis versus elective surgeries and establishing a relationship between manifest variables and distributive value index. METHODS: The volume of distribution was derived by a surrogate variable after extrapolating the concentration time decay curve in a graph by plotting TOF values on Y axis and time on X axis. RESULTS: The onset of action, duration of relaxant effect and recovery from anaesthesia was prolonged in peritonitis group compared to otherwise healthy group coming up for non-peritonitis surgery. CONCLUSIONS: All these findings can be explained by the assumption of hypothetical compartment attached to central compartment varies in its capacity and equilibration, depending on the prevailing level of hyperemia of the inflamed peritoneal compartment at any given point of time.

KEYWORDS: Atracurium, Peritonitis, Hyperemia, Distributive value index.

INTRODUCTION: Peritonitis is one of the most common cases that we encounter in the emergency theatre. There are many presentations coupled with peritonitis, like all the three stages of dehydration, shock, renal failure, metabolic acidosis or alkalosis, hypokalemia and systemic inflammatory response syndrome. Also in peritonitis, the volume of distribution of various substances is altered as there is a massive fluid shift across the surface of peritoneum due to its inflammation. Also because of systemic release of cytokines, microcirculation is altered affecting the effect site equilibration coupled with decreased effective blood flow to the organs of metabolism.1

Theoretically even the intrinsic clearance decreases and there is a third space loss, defined as such a volume loss that cannot be retrieved. Despite all these hemodynamic alterations, we dose the atracurium on basis of weight, which is not an appropriate method. Ideally speaking, any dosing of drug should be planned based on intravascular status of patient and volume of distribution. Given a fixed dose of drug that is given, the serum concentration of atracurium determines the volume of distribution. However, estimation of serum concentration cannot be done routinely, nor is recommended because of sophisticated equipment required (cost benefit analysis). Many institutions in our country lack this facility. One of the surrogate measures for measuring serum concentration of any neuromuscular blocking drug is noting the intensity of muscle relaxation that can be measured by peripheral nerve stimulator using a train of four pattern of stimulus.2,3 Assuming the goal of study, the recovery pattern is more important than providing the accurate degree of relaxation, ulnar nerve with monitoring of adductor pollicis is chosen. The TOF response either TOF count or TOF ratio is used for quantifying and comparison of neuromuscular relaxation. The present study compares the volume of distribution of...
a tracurium in peritonitis patients and healthy population using the train of four response of a peripheral nerve stimulator.⁴

MATERIALS AND METHODS: The present study “Volume of distribution of atracurium in different cohorts a comparative study” was undertaken at Osmania General Hospital, during period August 2009 to August 2011.

Prospective and comparative study was undertaken in the form of two groups, group A and group B. Each group consisted of 25 patients of either sex and ages between 20 to 60 yrs. Group A included all the patients posted for emergency laparotomy with ASA grade III E or IV E, whose provisional diagnosis was diffuse peritonitis. Group B included patients posted for elective surgeries where there is no expected major fluid shifts during surgery like mandible fracture, open reduction and internal fixation, nasal bones fracture correction, flap revision (<5%)- ASA grade II. All the selected patients were explained about the procedure and informed consent taken.

Inclusion Criteria:
- Patients aged between 20 to 60 years.
- No other comorbid condition except for the indication of surgery.
- Patients who have given informed consent.

Exclusion Criteria:
- Patients age <20yrs, >60 years.
- Patients who were seropositive for HIV or HBsAG.
- Patients with chronic diseases like hypertension, asthma, diabetes and atopic allergy.
- Patients with multi organ dysfunction syndrome or septic shock.
- Patients with peritonitis induced hyponatremia, renal failure, urine output <0.5 ml/kg.
- Patients with resuscitation resistant hypotension. – Patients with abnormal EKG, potassium disturbance.

Induction was based on the permissible status of the patient. This included one of the following Thiopentone sodium or Ketamine. The intubation was performed in emergency setting as rapid sequence with succinylcholine 1.5 mg/kg and after its complete recovery, Atracurium was given and ventilated, fluids and other drugs were similar for both the groups to obviate any error, due to different electrolyte pattern. Anaesthetic machine, resuscitation equipment and drugs were checked and kept ready, before undertaking any procedure.

Pre-operative assessment was done to ascertain whether the patient fits into the criteria or not and the procedure was explained and informed consent was taken. The patient’s vital signs were measured and optimized as much as possible, if any preload dependent hypotension was noted, it was resuscitated with colloids and crystalloids until a consistently normalized blood pressure was noted.

Temperature was monitored intraoperatively by using a probe in axilla and the maximum fall seen was 35.6 C, urine output was more than 0.5 ml/kg in all the patients. Subjects who had
less than 0.5ml/kg were excluded from the study to remove any confounding factor from kidney injury. If the blood pressure was suboptimal, the patients were classified as resuscitation resistant hypotension or septic shock and suitable vaspressors or ionotropes were started. These patients were excluded from the study. Before induction, the sites of electrode placement, 1 cm proximal to the junction of proximal most palmer crease of wrist and flexor carpi ulnaris, 2.5cms proximal to this site was cleaned with surgical spirit swab. After the sites are dried two EKG leads was attached. The negative electrode was attached distally and the positive electrode was attached proximally. A single twitch stimulation of 1 hertz was used to determine the current strength for supramaximal stimulation and the response of this stimulus is noted as to grade the intensity of TOF response post induction under atracurium relaxation.

The patient was induced and intubated. In emergency setting as Succinylcholine was used for rapid sequence intubation, the patient was not given Atracurium until he/she came out of the relaxation almost completely, while the patient was maintained at an adequate depth using inhalational anesthetics (0.5 – 1% isoflurane or 1- 2% sevoflurane).

Every five minutes the TOF stimulation was used to determine the intensity of neuromuscular blockade. It was graded by tactile and visual perception in accordance with the pre-induction single twitch response.

In case direct muscle stimulation was suspected, only adduction of Adductor Pollicis was taken into consideration. The TOF was stopped at TOF ratio of 0.4 unless the patient suddenly bucked at which the stimulation was stopped and top up was given. However, the patient was maintained on inhalational anesthetics until then. There were no instances of patient bucking before TOF <0.4.

RESULTS: Study includes 50 patients in each group of both males and females.

| Parameter    | Group A (Mean±sd) | Group- B (Mean±sd) |
|--------------|-------------------|--------------------|
| Age (years)  | 39.84±5.77        | 39.72±6.03         |
| Height (cms) | 161.32±3.89       | 161.16±3.73        |
| Weight (kgs) | 60.04±6.01        | 61.00±6.06         |

Table 1: Demographic data in the study

It can be inferred from the values in the table that there is no significant difference between group A and group B in terms of age, height and weight. The confidence interval value of age, height, weight in group A is 2.26, 1.52, 2.35 and that of group B is 2.36, 1.46, 2.37 considering their means, the ranges overlap indicating no significant difference. The p value of the students T test for age, height and weight is 0.94, 0.88 and 0.57 all of which are greater than 0.05, hence any differences between them is insignificant.
The confidence interval values of blood urea, serum creatinine, sodium and potassium of group A are 1.72, 0.05, 0.84, 0.083 and that of group B are 1.81, 0.05, 0.72 and 0.085. Considering their means, there is no significant difference between the two groups for blood urea, serum creatinine and potassium values as there are significant overlapping over the ranges of confidence intervals.

Regarding sodium, the confidence intervals in group A is 136.88±0.84 and that of group B 139.2±0.72 which in no way overlap, indicating a significant difference among the groups. Thus in peritonitis, though asymptomatic, many patients exhibited relative hyponatremia though clinically not significant. Furthermore, the above arguments can be confirmed by obtaining the p value from students T test. These values for blood urea, serum creatinine and potassium are 0.68, 0.76 and 0.896 which are higher than 0.05, thus no statistical difference. But the value for sodium is 0.00017, which is less than 0.05 making it statistically significant. Even if the probability alpha value is decreased to 0.01, the difference remains statistically significant.
Table 3: Primary outcome variables

| Parameter                | Group A (Mean±sd) | Group B (Mean±sd) |
|--------------------------|-------------------|-------------------|
| Onset of peak action(min)| 12.4±3.57         | 6.6±2.38          |
| Y' surrogate             | 17.88±0.78        | 22.08±0.70        |
| Duration (min)           | 46.72±3.94        | 25.28±2.40        |

The onset of peak action as defined in our study is the minimum time taken for the TOF count of zero to appear after the loading dose of Atracurium. In group A, the mean onset of the time was 12.4 minutes with confidence value of 1.39 where as that of group B is 6.6 minutes of mean onset with confidence value of 0.93, thus no overlapping means significance. The p value of students T tests return a value of 1.7*10^-8, which is far less than 0.05 assuming significance. Stated otherwise, the peak onset of atracurium is delayed in peritonitis.

Observation of the decay curve of atracurium in peritonitis revealed three different slopes so called alpha, beta and gamma phases. Alpha phase might represent the decay clearance of intravascular compartment; beta phase might represent the elimination phase. The third phase whose slope is almost parallel to alpha phase might represent the atracurium being sequestered in to the inflamed peritoneum, that returns to intravascular compartment as the plasma atracurium declines over time. The gamma slope also corresponded with the semi log transformed graph of the difference in extrapolated volume of distribution powered to alpha slope. In case of otherwise healthy patients the graph was similar to the standard first order kinetics, the distribution phase and elimination phase.

DISCUSSION: Peritonitis is one of the common acute abdomen that presents to our emergency operating room. It entails myriad of hemodynamic, metabolic compromise complicating as multi organ dysfunction syndrome. It starts with the toxins or irritant chemicals bathing the peritoneal cavity resulting in chemical peritonitis, especially due to hollow viscus perforation. Upon bacterial seeding, firstly polymorphonuclear leukocytes invade releasing eosinophilic granules and major cationic protein resulting in hyperemia of peritoneum and capillary leakage mediated by bradykinin. The peritoneal exudate thus formed dilutes the irritant toxin or decrease the bacterial density. This exudates is rich in plasma proteins and because of further increases in colloid osmotic pressure of inflamed peritoneum, significant fraction of intravascular volume transudates into the serosal cavity. This fluid accumulation is called third space loss defined as such volume loss that cannot be retrieved and does not participate in circulation.

Hence the total body water though is near normal, patients with peritonitis must be considered as intravascularly dehydrated. This fluid and protein loss reflex stimulates sympathetic nervous system of body and renin-angiotensin system. Yet the patient can have hypotension presenting as septic shock. As with any shock, end organ perfusion is hampered leading to anaerobic production of lactic acidosis. After 6 hours of inflammation, macrophages invade releasing IL-1, IL-6 and TNF-alpha, which stimulate T lymphocytes. Some of these cytokines get into circulation and set up systemic inflammatory response syndrome. These circulating cytokines
alter microcirculation at multi-organ level, thus though there is heightened metabolic oxygen demand, the oxygen extraction ratio is decreased. Thus the concept of beneficial effect of supra normal oxygen delivery. These circulating cytokines also vasodilate splanchnic and peripheral superficial vessels thus leading to wastage of significant fraction of cardiac output, at the same time, hampering vital organ perfusion.\textsuperscript{5}

The patient has decreased effective hepatic, renal and cerebral blood flow. Hence, there is a rationale for anesthetic drug titration in patients with peritonitis. Also with decreased effective clearance, the cytokines suffer excretion and delay in metabolism, with further accumulation, the patient enters into a vicious cycle of septic shock, leading to microcirculatory failure called multiorgan dysfunction syndrome. As intravascular volume is depleted with little change in total body water, proteins being exudated into peritoneum, the presence of hyper dynamic circulation, hyper metabolic response, altered microcirculatory pattern and its attended decreased vital organ perfusion. Pharmacology of many administered anesthetics is unpredictable and variable. Hence our study aimed at finding out some significant alterations that happen in these patients. Before the advent of Atracurium into clinical practice, a host of non-depolarizing muscle relaxants were used in the anesthetic management of peritonitis coming for exploratory laparotomy and closure of perforation. At first it was CURARE.\textsuperscript{6} Curare fell out of favors due to its notorious side effect of histamine release and consequent hypotension which can be lethal in peritonitis patients with compromised hemodynamics.\textsuperscript{7} Gallamine even though safe in liver disease, needed a fully functional kidney to excrete it. As many patients with peritonitis and septic shock have a pre-renal azotemia and compromised renal function and clearance, delayed recovery is the rule than an exception.\textsuperscript{8}

Introduction of Pancuronium as a muscle relaxant into clinical anesthetic practice provided some sort of solace in that there was minimal or negligible histamine release and intact somewhat enhanced sympathetic tone leading to better maintenance of hemodynamics during laparotomy. Pancuronium also was unique in that it had two channels of excretion viz. hepatic and renal and this was a welcome experience, considering that many of these peritonitis patients had either a hepatic or a renal compromise or at times both. So, the safety margin for Pancuronium was significantly better than Curare and Gallamine. Vecuronium was the next best thing to happen to these patients, because of its excellent hemodynamic profile and short acting nature and dual excretion through liver and kidney. But our clinical experience in the past showed that even Vecuronium was not fool proof and delayed recovery from anesthesia still happened occasionally. This was probably due to the fact that excretion into bile is an important way of elimination of Vecuronium.\textsuperscript{9} In septic peritonitis, the hepatic metabolism most of the times, is sluggish due to reduced hepatic blood flow both via portal vein and hepatic artery.\textsuperscript{10} Sluggish excretion of bile due to cholestasis also contributes to delayed recovery. Many of the duodenal perforations, ileal perforations and enteric fever perforations patients are dehydrated and invariably present at some time or other with a clinically manifest hypokalemia and paralytic ileus. Hence it's no wonder that these patients also have a delayed recovery from anesthesia at the end of surgery, necessitating prolonged ventilation and critical life support.

The advent of Atracurium into clinical practice is the near best answer that anesthetic services have provided to such critically ill patients with a compromised safety.\textsuperscript{11} Here is a unique
muscle relaxant, not influenced whatsoever by the hepatic and renal metabolism or clearance by them. Most of the clinical conditions are metabolized by non-specific esterases, Hoffman’s elimination and liver. A unique process HOFFMAN degradation is a pH sensitive splitting of drug by the plasma esterases as drug travels through various compartments of body and comes across varying pH environments. This process does not require an intact liver and kidney and needs only the presence of blood in human body. Hence, even anephric patients can be assumed of a hassle free recovery from the drug. Hence Atracurium is chosen in this study.

On statistical analysis of this study results, the patients with peritonitis have a generalized tendency to relative hyponatremia due to avid retention of water by kidney and salt sequestration in third space. The hemo concentration is because of fluid shifts and tachycardia because of hyperdynamic circulation induced by cytokines. The analysis of primary outcome variables reveal that there is a significant delay in the onset of peak action of atracurium in patients with peritonitis (mean: 12.4 min) compared with otherwise healthy patients (mean 6.6 min).

The onset of peak action as defined in our study is the minimum time taken for the TOF count of zero to appear after the loading dose of Atracurium. By extrapolating the decay curve backwards, a surrogate of plasma concentrations of Atracurium were obtained and it was found that the central volume of distribution of atracurium was increased in patients with peritonitis. Similarly the prolongation of duration of action in peritonitis (mean: 46.72 min) compared with otherwise healthy population (mean 25.28 min). The difference in the extrapolated volume of distribution when plotted along the semi log transformed graph closely corresponded with the gamma phase of the decay curve.

The volume of distribution divided by body weight is called distributive value index. Observation of the decay curve of atracurium in peritonitis revealed three different slopes so called alpha, beta and gamma phases. Alpha phase might represent the decay clearance of intravascular compartment, beta phase might represent the elimination phase. The third phase whose slope is almost parallel to alpha phase might represent the Atracurium returning to intravascular compartment from the inflamed peritoneum into which the drug has sequestered before. The gamma slope also corresponded with the semi log transformed graph of the difference in extrapolated volume of distribution powered to alpha slope.

The prolonged duration could also be due to the prevailing metabolic acidosis with poor end organ perfusion. In case of otherwise healthy patients the graph was similar to the standard first order kinetics, the distribution phase and elimination phase. This might explain the observation that initially when the loading dose of Atracurium (> 0.5 mg/kg) is given, the drug is first sequestered in the difference in extrapolated volume of distribution powered to alpha slope. The prolonged duration could also be due to the prevailing metabolic acidosis with poor end organ perfusion. In case of otherwise healthy patients the graph was similar to the standard first order kinetics, the distribution phase and elimination phase. This might explain the observation that initially when the loading dose of Atracurium (> 0.5 mg/kg) is given, the drug is first sequestered in the peritoneal vessels because of hyperemia and only a third or half is available for neuromuscular blockade. Recirculation must take place in order to reach the peak levels. Also because of altered microcirculation pattern, there may not be optimum effect site equilibrium. All these might explain the delayed onset of peak action and increased central volume of
distribution. As the hyperemia of peritoneal wall decrease, as resuscitation measures continue, that approximately occurs around 15-20 minutes in to peritoneal cavity is not a third space loss as it occurs for fluid and proteins, but essentially a different compartment of intravascular volume that changes its speed of equilibrium depending on the inflammatory response.\(^{14,15}\)

The delay in onset could also be because of decreased end organ perfusion and increased duration could also be explained by prevailing metabolic acidosis. However the parallelism between alpha and gamma curves might represent a different compartment than acidosis. Though there is a positive correlation (correlation coefficient of + 0.894, closer to +1), between relative hyponatremia, hemoconcentration and tachycardia, no quantitative relationship could be established. The presence of these variables might just indicate altered pharmacokinetics and not by how much. Thus the relationship between manifest variables and distributive value index (defined as volume of distribution divided by weight in kgs) cannot be explained.

**CONCLUSION:** From our study, it is obvious that the onset of action, duration of relaxant effect and recovery from anesthesia was prolonged in peritonitis group compared to otherwise healthy group coming up for non-peritonitis surgery. In patients with peritonitis, the peak onset of action of atracurium is delayed, central volume of distribution is increased and duration of action prolonged. All these findings can be explained by the assumption of hypothetical compartment attached to central compartment varies in its capacity and equilibration, depending on the prevailing level of hyperemia of the inflamed peritoneal compartment at any given point of time. The prolonged duration of action of atracurium in the peritonitis group and subsequent recovery could also be due to sluggish metabolism of atracurium in acidic environment, which slows down not only the Hoffman’s degradation but also non-specific esterases and hepatic clearance. All the pre-operative indices were comparable except for relative hyponatremic tendency, hemoconcentration and tachycardia in patients with peritonitis compared with otherwise healthy patients. Although sodium levels, hemoconcentration and tachycardia, the so called manifest variables indicate that there is altered pharmacokinetics in patients with peritonitis, no quantitative relationship could be established between manifest variables and distributive value index.

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Date of Submission: 06/09/2015.
Date of Peer Review: 07/09/2015.
Date of Acceptance: 10/09/2015.
Date of Publishing: 18/09/2015.