500 Years after Curares Discovery: What has Changed, What has not?

Massimiliano Sorbello[1,*], Ivana Zdravkovic[2] and Radmilo Jankovic[3]

[1]*Department of Anesthesia and Intensive Care, AOU Policlinico Vittorio Emanuele, Catania, Italy*

[2]*Department of Anaesthesia and Reanimation, Clinical Hospital Center "Zvezdara", Belgrade*

[3]*Center for Anaesthesiology and Reanimatology, Clinical Center of Niš; School of Medicine, University of Niš, Serbia*

Abstract: Curares were first discovered in 1500's by pioneering explorer which were perfectly aware of their use as poisons but completely unaware of their potential as medications; it was to wait until late 1800's to know some more on them, and only in middle 1940's some medical applications started, resulting in important evolution towards modern anesthetic techniques, including balanced anesthesia and opportunity for more complex surgical procedures. New molecules, meaning new problems, including Postoperative Residual Curarization (PORC), anesthesia awareness, difficult airway management and related clinical problems. Many advancements have been performed in the last 50 years, new molecules are available and new opportunities for powerful, fast and effective antagonism are available. Nevertheless, curares remain poisons, and their use could be considered safe only in experienced hands, not less than native americans Men of Medicine, and always taking account of situation, strategy and patients characteristics before counting on onset, offset and possibility for reversal. All points showing that in 500 years many things changed and many others they probably remained the same, because in the end, it is not the drug, but the man who gives it.

Keywords: Intubation, muscle relaxants, reversal, postoperative residual curarization.

If we want things to stay as they are, things will have to change.

G T di Lampedusa, "The Leopard"

1958, Feltrinelli

1. AN EYE TO THE PAST

Poisons exerted some fascination on Man since the beginning of time, and in certain sense, the most the poison was misterious and exotic, the most it was at same time fascinating and scaring. Use of poisons we find in Mythology, in tales, in historical attempts for assassinations, in comedies and tragedies, and last but not least in Medicine. And as Lee stated [1], poisons conveyed a sense of power to the poisoner and a sense of fear and impotence in the observer. In a certain sense, this observation from Dr Lee, perfectly fits to curare as poison, and perfectly depicts relationship between Anesthetists and Neuromuscular Blocking Agents (NMBAs), if not for difference that they are not used any more for hunting and that they should not be used for homicide!

History of NMBAs is fascinating, starting in far 16th century: Explorers of South America returned with tales of Native Indian arrow poisons that could kill enemies and animals during hunting, so that Pietro Martire D'Anghiera named this mysterious substance as *flying death* in his chronicles [2]. Today we know that venom was extracted from plants as *Chondrodendrum spp* and *Strychnos spp*, but this idea at that time it was completely unknown, and we had to wait until 1594 when Keynes, one of attendants of Sir Walter Raleigh (famous English explorer, merchant venturer, poet, and mostly known for diffusion of tobacco in Europe from New World) came back from what we name today Venezuela with few samples of some mysterious venom for which the same Keynes and Raleigh suggested use of garlic as antidote in case of contact with this terrible poison.

Once back in Europe, they named as native americans did: *ourari*.

As a curiosity, in original language, the word *ourari* came fron *uira* (kill) and *ery* (bird), and once diffusion in Europe started, these farly unknown substances were named in most different ways: *ourara* (Brodie, 1811)*, urali, woorari, wouralia* (Waterton, 1812), *urare* (Schomburgk 1841)*,* and finally *curare* [3]. Between 1500 and 1700 small samples were brought to Europe by many explorers in search for adventure (Bartolome de las Casas, the Apostle of the Indians, D'acuna, Oviedo, Herra, Gumilla, and Gomora)[1], but most of them reported of legends and use and preparation by native Americans, and it is lot of opened questions

*Address correspondence to this author at the Anesthesia and Intensive Care, AOU Policlinico – Vittorio Emanuele University Hospital 687, *Via* Del Plebiscito – 95100 Catania, Italy; Tel: +39 349 6277107;
E-mail: maxsorbello@gmail.com

E-ISSN: 2310-9394/15

which do remain unanswered still today: how did the American Indians discover the terrible poison for their arrows? Was it some casual discover? Was it some accidental poisoning? Or some magician tradition brought from fathers to sons? What we know for sure is that those who knew the secret were given an important social status, with recognised and feared power, and they were named as *medicine men*, the few elected that could recognise the danger in manipulation and preparation of the poison. In this social system, women (and particularly menstruating ones) were absolutely excluded, whereas history taught us that just venoms became the preferred instrument for some dangerous women curses and revenges all along history!

Charles Marie de la Condamine described some experiments with *black pitch* in 1740, and only in 1804 Charles Waterton succeeded to obtain large amount of *ourari* samples and to try them in animals (so he gave a donkey, since then named *Wouralia*, the honor of History) [4]. Sir Benjamin Brodie tried curare on small animals (cats) in 1814, demonstrating its lethal effect, its parenteral mechanism of action and the opportunity to maintain the animal alive artificially inflating his lungs with a bellow [5]. In 1846 Claude Bernard, demonstrated in a frog that curare was acting on neuromuscular junction, providing first structured and extensive information on this new drug's characteristics: that there was no adsorption through intestine and effect was only if poison entered bloodstream, that death was due to respiratory failure with no direct influence on heart, and that only neuromuscular junction was effect site for poison. Same year, coincidence, on October 16th, W.T.G. Morton gave first public demonstration of Anesthesia in Boston. In 1860's T.R. Fraser and A.C. Brown produced quaternary amines (synthesis curares), in 1934 H. Dale discovered acetylcoline and neuromuscular transmission [6], and more or less in that time H. King isolated tubocurarine, so called because he obtained samples by "curare in a tube" from a Museum piece more than one hundred years old [7].

Therapeutical use of curares started in 1941, when American Psychiatrist Abram E Bennet, on suggestion of Dr McIntyre, he first (and successfully) used curare to reduce incidence of bone fractures during electroconvulsive therapy with metrazol, presenting his work during 91st annual session of the American Medical Association [8]. Interestingly, couple of years before, Gill, who had just known of his multiple sclerosis, offered 12 kg of raw curare samples of *C. Tormentosum* from Ecuador to ER Squibb & Sons: here, pioneering work from Mr Holaday, lead to isolation of pure *d-tubocurarine*, and trade name *Intocostrin* was given to this new molecule, launched on market in 1942 and changing for ever Anesthetists tasks, workflow and worryings (picture **1**).

Picture 1: Some pieces of curare history: from top left samples of modern curares, poisoned arrows and *black pitch*, reproduction of aancient map and *de orbe novo* and *intocostrin* original package.

Not a case, on 23 january 1942 H.R. Griffith, an enthusiastic Anaesthetist at Homeopatic (!) Hospital in Montreal, expert with the "new" (at that time) technique of endotracheal intubation, first used curare for airway control, asking his resident E. Johnson, to inject *Intocostrin* to a young lady undergoing appendicectomy in general anaesthesia with tracheal intubation, following with a report published in the same year on 25 patients [9].

One year later, Cummins reported the first 3000 patients treated with Intocostrin +/- thiopental to control drug induced convulsions [10], and in 1947 T.C. Gray and Colleagues reported use of *Intocostrin* for General Anaesthesia in a large series of 8500 patients with "*no attributable deaths*" [11], underlining that main benefit from this new drug was improving operating conditions for surgeon and for what we call today "*surgical space*" [12-13]. Work from Dr Gray provided large contribution for use and understanding of curare, changing the perspective on Anesthetists' point of view. In a famous lecture delivered in 1947 at the Royal College of Surgeons of England [14], he listed main benefits of introducing curare in Anesthetic technique:

(1) To provide, using only very light anaesthesia, the muscular relaxation which is required for abdominal surgery;

(2) To facilitate, in a light plane of anaesthesia, control of the respiration during thoracic operations;

(3) To ensure freedom from laryngeal spasm during any anaesthesia;

(4) To potentiate the anaesthetic agents so that light anaesthesia can be maintained with only minimal quantities.

and, introducing the so called "*Liverpool technique*", he officially opened new era of *balanced anesthesia* [15-16]: surgery became safer, because no more high doses of ether or barbiturate were necessary to obtain muscle relaxation, and pharmacological load of anesthesia was split in different molecules, making the triad of hypnosis, analgesia and muscle relaxation how we still use it today:

[…]This is essentially a balanced anaesthesia. After induction the patient is maintained in a light plane by means of an intrave- nous barbiturate. The curarine produces relaxation and at the same time so reduces the amount of the barbiturate which has to be used that there is no delay in recovery. The exhibition of any of the inhalational agents is possible without causing laryngeal spasm. […] With very little experience the quantity of the barbiturate, the curarine, and the inhalational anaesthetic can be so estimated that no excessive amounts of any single one of them will produce a delay in post-operative recovery.... Experience has shown that this balanced technique results in far less post-operative morbidity than if the anaesthesia were either solely inhalational or solely intravenous.

Pharmaceutical research moved in those years important steps: in 1949 WMD Paton and EJ Zaimis synthetically developed an histamine releasing curare, naming it *decamethonium* [17], and finally, within 1947 and 1949, contemporary work from three groups (Italy, England and US) led to synthesis of *Gallamine* by D. Bovet. In 1949 he published first study on *succynilcholine*, and he was awarded with Nobel Prize in 1957 for his contribution to Neuropharmacology.

Despite being first synthetized in 1909, *succynilcholine* entered modern anesthetic pharmacology only in 1951 as *Anectine* or *Quelicine* [18]; and exactly ten years later, in 1961, B.A. Sellick published his milestone paper on *Cricoid Pressure*, *Rapid Sequence Induction* and *aspiration pneumonia* prevention [19].

On this timeline, many other molecules were synthetized: Jacob Pal described antagonism of curare with *physostigmine* yet in 1900, whereas *neostigmine* (10 times more effective) was produced only in 1931; *Pancuronium* was released in 1964, *Vecuronium* in 1979, *Atracurium* in 1985, Doxacurium in 1988, *Mivacurium* in 1993, *Cisatracurium* in 1996, *Rocuronium* in 1994 and finally in 2008 *Sugammadex*, a revolutionary antagonising molecule. And way for research is far to be ended [20-21] (picture **2**).

2. TWO EYES ON THE PRESENT

Introduction of NMBAs in clinical practice of Anesthesia, as above mentioned, if on one side changed completely surgical approach with unbearable benefit, on other hand resulted in appearance of two new important issues: what we do call today *awareness*, that is risk of too light anesthetic plan

	Onset/duration of action	Ganglion blockade	Histamine release	Cardiac effects	Elimination
Tubocurarine	Slow/long	Yes +++	Yes +++	Hypotension	Renal
Gallamine	Slow/long	No	No	Tachycardia	Renal
Pancuronium 1964	Slow/long	No	No	Tachycardia	Renal/hepatic
Vecuronium 1975	Slow/intermediate	No	No	Nil	Hepatic/renal
Atracurium 1981	Slow/intermediate	No	Yes +	No	Hofmann
Mivacurium 1986	Slow/short	No	Yes +	No	Plasma cholinesterase
Rocuronium 1988	Rapid/intermediate	No	No	No	Hepatic/renal

Picure 2: Main characteristics and year of introduction of modern curares.

covered by contemporary administration of NMBAs, and beginning of airway management era (and difficult airway management nightmare), due to capability of these powerful drugs to suppress spontaneous breathing.

First problem is awareness, risk of too light anesthesia which remains unrecognized because of paralysing effect from NMBA. Results are catastrophic, with serious complications for patients including post traumatic stress disorder, and dimension of the problem is often underestimated.

Not recent studies extimated incidence in over 26,000 cases/year in USA [22], and recently published NAP5 (National Audit Project 5) [23] in UK numbered incidence of certain/probable and possible accidental awareness cases in ~1:19,600 anaesthetics. Not surprisingly, same paper clearly indicated that incidence with neuromuscular block was ~1:8200, whereas without it was ~1:135,900.

Checklists use, wise use of medications, experienced approach to anesthesia and use of anesthesia depth monitors seem to be able to reduce occurrence of this phenomenon, which remains conceptual though obvious side effect of use of NMBAs.

Second problem is relationship with airway management: on more than 500 years of history, curares and airway management entwined their destinies only in the last 70 years (picture **3**), but so many things they were able to change, and new issues they raised.

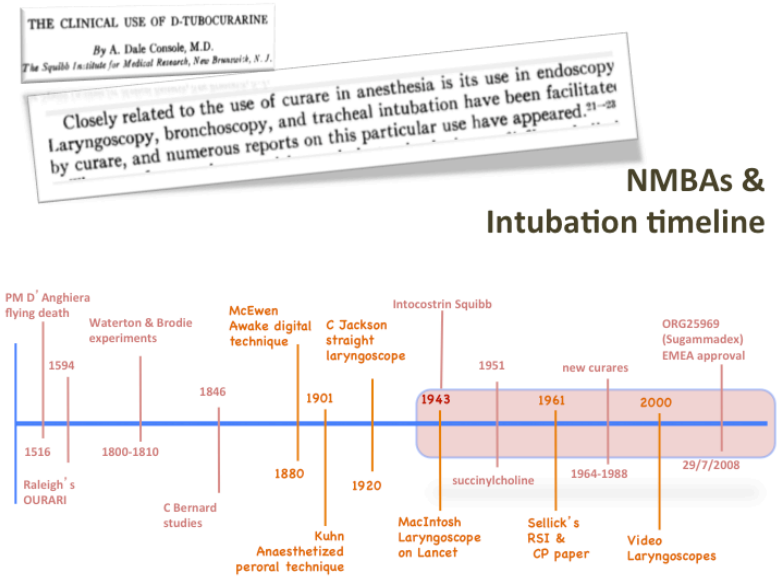
In fact, on one hand NMBAs allowed dramatic improvement in airway management techniques, starting from point that they finally allowed more atraumatic intubation, they widened opportunities for surgery by making Anesthesia safer thanks to the concept of *balanced anesthesia*.

But there is also the dark side of the moon, perfectly summarized in TC Gray's [14]:

Curare should never be used by anyone who is not fully conversant with the care of the apnoeic patient. Anoxia appears easily and is more serious, especially when there is cardiac inefficiency […]. We [offer] a grave and insistent warning to the inexperienced that we are dealing with one of the most potent poisons known.

It is widespread accepted that use of NMBAs makes intubation safer, less traumatic and easier [24], despite a certain degree of complications and laryngeal consequences do remain independently on NMBAs administration, just like if intubation per se could be some "not so safe" manouver [25]. Conversely, whenever difficult airways are encountered, with particular reference to difficult mask ventilation and difficult oxygenation [26], uncautios NMBAs administration could turn into no exit road, the so called *cannot intubate-cannot oxygenate scenario*, with deadly consequences.

Independently on, and before, airway management guidelines [27], the Holy Graal for expected (or at risk)



Picture 3: Timeline of curares discovery and evolution and airway management key events.

difficult airways was represented, and someway it is still, by *succynilcholine*. This drug, with fast onset and fast recovery, allowed a different approach to airway management, someway granting an escape plan in case of unexpected or predicted difficulties. Same molecule allowed preoxygenation and rapid sequence intubation strategies [28], and for many years, more than 50 after its introduction, it represented safe harbor and unchangeable certainty for almost majority of Anesthetists. But, unfortunately, in many cases it was just an illusion.

Sellick manoeuver, cricoid pressure seem to be unuseful if not detrimental in case of (difficult) airway management [29], and *succynilcholine* has been claimed for many side effects including lethal events, and almost 60 years after introduction in clinical practice, even if it is still (more or less) largely used, its role has never been so deeply in discussion as it is now, making it one of the most controversial drugs in hands of Anesthetists. Most reliable objection to its administration for predicted difficulties is that despite fast offset, as demonstrated in many papers [30], critical desaturation might occurr, because of interindividual variability, clinical context, comorbidities and coadministration of analgetics/hypnotics for anesthetic induction [31]. This means that idea of being back safely to spontaneous breathing in case of failed airway was merely illusion; similarly, results from NAP4 (National Audit Project 4) [32], showed that aspiration remains between first causes of mortality and morbidity in anesthesia practice, lighting up the point that probably that Holy Graal we thought to have in our hands, it is not.

Today, new drugs are available and they seem to have opportunity to depict completely new scenario: development of *sugammadex*, first selective relaxant-binding agent, could have opportunity to change the Story, and when used to reverse rocuronium it is actually best performing alternative if compared with other reversal strategies [33], for use in rapid sequence intubation [34-35] and with time to desaturation in respect with succynilcholine, including obese patients [36], allowing the surgeon dream of “relaxation until last stitch”.

Unfortunately, after initial enthusiasm, some concerns started to come out with possible side effects on postoperative coagulation due to sugammadex administration [37], and many more on real opportunity to reverse a critical cannot intubate-cannot oxygenate using *sugammadex* even in high doses [38-40].

Lee enthusastically wrote *Goodbye suxamethonium!* [41], but while demonstrating fast and complete recovery on neuromuscular monitoring after *sugammadex* administration to reverse rocuronium, his study did not measure the pure time to return to spontaneous breathing nor he did describe doses of other drugs used for anesthesia induction, and as we know [30-31], return to spontaneous ventilation yet in absence of neuromuscular blocking drugs could be delayed after even modest doses of propofol and an opioid.

In the end, despite great opportunity offered by *sugammadex*, it could be valuable in certain number of patients but not in all, accordingly to underlying comorbidities and parameters for difficult ventilation and/or intubation, and all this not taking account of economic implications linked to “routine” use of rocuronium-sugammadex combination [42]. As a result, availability of highly effective and safe reversal strategy, should never replace planning of preprocedural strategy and focused use accordingly to clinical needs and patients characteristics [43].

Other side effect due to NMBAs administration is the so called Postoperative Residual Curarization (PORC): it has been largely underestimated, and some reports do show dramatic numbers in post anesthesia care units, ICUs and postsurgical wards, with life-threatening and safety implications of patient postoperative course [44-46] while very recent studies show that use of sugammadex could reduce or reduce to zero incidence of PORC in ICU [47].

Basically, knowledge and awareness of PORC came out after widening and diffusion of neuromuscular block monitoring: firstly described yet in 1958 [48], NMBAs activity monitoring are becoming only in last 5 to 10 years a standard part of anesthesia monitoring equipment, adding an important level of criticity and safety to Perioperative Medicine.

Old Steward criteria [49] for extubation readiness should be abandoned, and routine neuromuscular monitoring should be the rule, extubation readiness judged on T4/T1 TOF ratio of 0.9 [50-51]: only this approach could make use of NMBAs safer and complication rates lower, indicating once more that

unexperienced use of curares still makes them dangerous as poison they were discovered.

3. ONE EYE TO THE FUTURE

Seventy years after *Intocostrin*, muscle relaxation continues to play a key role in anesthesia practice, and unstoppable progress is moving in all basic and clinical aspects of neuromuscular pharmacology and monitoring. Unfortunately, the "perfect muscle relaxant" is still not in our hands, and we should also consider hypothesis it might never be.

The challenge for future with NMBAs is development of new drug with optimal risk/effectiveness and cost/benefit ratios, but at same time standardization of routine use of instruments for neuromuscular block monitoring, to allow patient tailored administration of NMBAs aiming to highest safety standards.

Many points remain to work on: rapid sequence induction, establishment of precise rules and criteria to address administration of whatever NMBA, but fastly reversible, against opportunity to maintain spontaneous breathing (as for example with fiberoptic awake intubation) in case of predicted difficult airways, also considering intriguing opportunity offered by new anesthetic molecules to seek for endotracheal intubation without NMBAs [52-53].

New drugs are continuously researched and developed [51], and probably in next future we will have opportunities which we do not even consider today; but for that time we should never forget how to use wisely prevention strategies and we should find answer to real questions: one example above all is recent attention on surgeons' need for *surgical space*, especially taking account of modern laparoscopic and robotic techniques [13]. This need has moved attention towards *deep block* techniques, with higher NMBAs doses or closer administrations, with attention to advanced neuromuscular monitoring techniques such as *double burst stimulation* and *post-tetanic count*, whereas the unanswered question is still if perfect operatory conditions do really depend upon muscle relaxation state or on other factors [54-55] first of all on Surgeon's performance and on anesthesia quality.

4. WHAT CHANGED IN 500 YEARS?

Many things changed since first reports from Pietro D'Anghiera on *flying death*, and probably some others remained completely unchanged. Differently than 500 years ago, we do today know what the *black pitch* is, we know exactly how it works, we produce new and better performing molecules with even more captivating names of those given in the past by the fantasy of explorers and bothanics.

And we are also able to produce reversal agents to counteract NMBAs effects and their critical therapeutical index, which is equal to zero, considering that effective dose is equal to lethal one.

Today it is not only male subjects and *Men of Medicine* to produce or work with curares, and it is not anymore only large or small size animals with original names to be given NMBAs, as they became, and with full reason, fundamental and rarely avoidable part of any general, or better *balanced*, anesthetic technique.

Curares changed Anesthesia, they unexpectedly and dramatically raised safety standards allowing drug combination in general anesthesia, and, not less valuable, they also made good surgeons happy and poor surgeons happier.

But at same time, they opened new frontiers and they raised new and unexpected problems, such as awareness and *cannot intubate-cannot oxygenate scenario*, recalling back anesthetists and researchers to find new strategies and new solutions respectively.

Story of curares is, intriguing, and it is perfect metaphor of unstable equilibrium; they are part of our daily practice as Anesthetists, we use them often being unaware of how long and fascinating story is behind the small glass *via*l that we open, and at same time equally unaware there will be some day in our career they will be like in Shirley Bassey famous song "*… impossible to live with you, but i could never live without you*" [56].

Because curares, 500 years later, they remain poisons, so they require experienced hands, not less than precise and unbeatable hands of poisoned arrows throwing Native Americans.

And again because, as stated by Sir Ian Robert Macintosh, inventor of Macintosh laryngoscope (curiously, in same year of *Intocostrin* being launched on the market), *It is not the drug that is dangerous, but the man who gives it.*

REFERENCES

[1] Lee MR. Curare: the South American arrow poison. J R Coll Physicians Edinb 2005; 35: 83-92.

[2] D'Anghera PM. De Orbe Novo 1516. MacNutt FA (Translator). New York: Putnams 1912.

[3] McIntyre AR. Curare: Its History, Nature and Clinical Use. Chicago, Illlinois: University of Chicago Press 1947.

[4] Smith WDA. Waterton and Wouralia. Br J Anaesth 1983; 55: 221-5. http://dx.doi.org/10.1093/bja/55.3.221-a

[5] Brodie BC. Further experiments and observations on the action of poisons on the animal system. Phil Trans R Soc Lond 1812; 102: 205-27. http://dx.doi.org/10.1098/rstl.1812.0013

[6] Dale HH. Chemical transmission of the effects of nerve impulses. BMJ 1934; 835. http://dx.doi.org/10.1136/bmj.1.3827.835

[7] King H. Curare alkaloids: 1, tubocurarine. J Chem Soc 1935: 1381-89. http://dx.doi.org/10.1039/jr9350001381

[8] Bennett AE. Curare: a preventive of traumatic complications in convulsive shock therapy. Amer J Psychiat 1941; 97: 1040-2. http://dx.doi.org/10.1176/ajp.97.5.1040

[9] Griffith HR, Johnson GE. The use of curare in general anaesthesia. Anesthesiology 1942; 3: 418-20. http://dx.doi.org/10.1097/00000542-194207000-00006

[10] Cummins JA. Experience with 3,057 administrations of curare to 232 psychotic patients treated with metrazol. Psychiat Quart 1943; 17: 655-70. http://dx.doi.org/10.1007/BF01561845

[11] Gray TC. d-Tubocurarine Chloride. Proc Roy Soc Med l948; 41: 559-61.

[12] Dale Console A. The clinical use of D-tubocurarine. Annals of the New York Science Academy; 1951: 53: 498-502. http://dx.doi.org/10.1111/j.1749-6632.1951.tb39939.x

[13] Staehr-Rye AK, Rasmussen LS, Rosenberg J. Surgical Space Conditions During Low-Pressure Laparoscopic Cholecystectomy with Deep Versus Moderate Neuromuscular Blockade: A Randomized Clinical Study Anesth Analg 2014; 119 (5): 1084-92. http://dx.doi.org/10.1213/ANE.0000000000000316

[14] Gray TC. The use of d-Tubocurarine chloride in anaesthesia: lecture delivered at The Royal College of Surgeons of England on 17th April, 1947. Ann R Coll Surg Engl 1947; 1: 191-203.

[15] Gray TC, Halton J. Technique for the use of d-Tubocurarine chloride with balanced anaesthesia. Br Med J 1946; 4: 293-5. http://dx.doi.org/10.1136/bmj.2.4469.293

[16] Shafer SL. From d-tubocurarine to sugammadex: the contributions of T. Cecil Gray to modern anaesthetic practice. Br J Anaest 2011; 107(1): 97-102. http://dx.doi.org/10.1093/bja/aer117

[17] Paton WDM, Zaimis EJ. The pharmacological actions of polymethylene-bistrimethyl-ammonium salts. Br J Pharmacol 1949; 4: 381.

[18] Dorkins, R. "Suxamethonium - The development of a modern drug from 1906 to the present day". Med Hist 1982: 26; 145-168. http://dx.doi.org/10.1017/S0025727300041132

[19] Sellick BA. Cricoid pressure to control regurgitation of stomach content during induction of anaesthesia. Lancet 1961; 19; 2(7199): 404-6.

[20] Naguib M, Brull SJ. Update on neuromuscular pharmacology. Current Opinion in Anaesthesiology 2009; 22: 483-490. http://dx.doi.org/10.1097/ACO.0b013e32832b8cff

[21] Lien CA. Development and potential clinical impairment of ultra-short-acting neuromuscular blocking agents. Br J Anaesth 2011; 107(51): i60-i71. http://dx.doi.org/10.1093/bja/aer341

[22] Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, Gan TJ, Domino KB. The incidence of awareness during anesthesia: a multicenter United States study. Anesth Analg 2004; 99(3): 833-839. http://dx.doi.org/10.1213/01.ANE.0000130261.90896.6C

[23] Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N *et al.* Royal College of Anaesthetists; Association of Anaesthetists of Great Britain and Ireland. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth 2014; 113(4): 549-59. http://dx.doi.org/10.1093/bja/aeu313

[24] Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Gatke MR, Wetterslev J and the Danish Anaesthesia Database. Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103 812 consecutive adult patients recorded in the Danish Anaesthesia Database. Br J Anaesth 2009; 103(2): 283-90. http://dx.doi.org/10.1093/bja/aep124

[25] Mencke T, Echtemach M, Kleinschmidt S, Lux P, Barth V, Plinkert PK, *et al*. Laryngeal morbidity and quality of tracheal intubation. A randomized controlled trial. Anesthesiology 2003; 98: 1049-1056. http://dx.doi.org/10.1097/00000542-200305000-00005

[26] El-Orbany M, Woehlck J. Difficult Mask Ventilation. Anesth Analg 2009; 109: 1870-80. http://dx.doi.org/10.1213/ANE.0b013e3181b5881c

[27] Frova G, Sorbello M. Algorithms for difficult airway management: a review. Minerva Anestesiologica 2009; 75(4): 201-209.

[28] Stept WJ, Safar P. Rapid induction/intubation for prevention of gastric-content aspiration. Anesth Analg 1970; 49: 633-6. http://dx.doi.org/10.1213/00000539-197007000-00027

[29] Maltby JR and Beriault MT. Science, pseudoscience and Sellick. Can J Anesth 2002 (49); 5: 443-447. http://dx.doi.org/10.1007/BF03017917

[30] Heier T, Feiner JR, Lin J, Brown R and Caldwell JE. Hemoglobin Desaturation after Succinylcholine-induced Apnea. A Study of the Recovery of Spontaneous Ventilation in Healthy Volunteers. Anesthesiology 2001; 94: 754-9. http://dx.doi.org/10.1097/00000542-200105000-00011

[31] Stefanutto B, Feiner JR, Krombach J, Brown R and Caldwell JE. Hemoglobin desaturation after propofol/remifentanil-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. Anesth Analg 2012; 114: 980-6. http://dx.doi.org/10.1213/ANE.0b013e31824e5bc4

[32] Cook TM, Woodall N and Frerk C. On behalf of the Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: Anaesthesia.British J Anaesth 2011; 106(5): 617-31. http://dx.doi.org/10.1093/bja/aer058

[33] Flockton EA, Mastronardi P, Hunter JM, Gomar C, Mirakhur RK and Aguilera L *et al*. Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine. Br J Anaesth 2008; 100(5): 622-30. http://dx.doi.org/10.1093/bja/aen037

[34] Sluga M, Ummenhofer W, Siegemund M and Marsch C. Rocuronium Versus Succinylcholine for Rapid Sequence Induction of Anesthesia and Endotracheal Intubation: A Prospective, Randomized Trial in Emergent Cases. Anesth Analg 2005; 101: 1356-61. http://dx.doi.org/10.1213/01.ANE.0000180196.58567.FE

[35] Sørensen MK, Bretlau C, Gatke MR, Sørensen AM and Rasmussen LS. Rapid sequence induction and intubation with rocuronium–sugammadex compared with succinylcholine: a randomized trial. Br J Anaesth 2012;

108(4): 682-9.
http://dx.doi.org/10.1093/bja/aer503

[36] Tang L, Li S, Huang S, Ma H and Wang Z. Desaturation following rapid sequence induction using succinylcholine vs. rocuronium in overweight patients. Acta Anaesthesiol Scand 2011; 55: 203-208.
http://dx.doi.org/10.1111/j.1399-6576.2010.02365.x

[37] Rahe-Meyer N, Fennema H, Schulman S, Klimscha W, Przemeck M and Blobner M *et al*. Effect of Reversal of Neuromuscular Blockade with Sugammadex versus Usual Care on Bleeding Risk in a Randomized Study of Surgical Patients. Anesthesiology 2014; 121: 969-77.
http://dx.doi.org/10.1097/ALN.0000000000000424

[38] Curtis R, Lomax S and Patel B. Use of sugammadex in a 'can't intubate, can't ventilate' situation. Br J Anaesth 2012; 108(4): 612-14.
http://dx.doi.org/10.1093/bja/aer494

[39] Kyle BC, Gaylard D and Riley RH. A persistant 'can't intubate, can't oxygenate' crisis despite rocuronium reversal with sugammadex. Anaesth Intensive Care 2012; 40: 344-346.

[40] Van Gestel L and Cammu G. Is the effect of sugammadex always rapid in onset? Acta Anaesthesiol Belg 2013; 64(2): 41-7.

[41] Lee C. Goodbye to suxamethonium! Anaesthesia 2009; 64: 73-81.
http://dx.doi.org/10.1111/j.1365-2044.2008.05873.x

[42] Fuchs-Buder Ta, Meistelman C and Schreiber JU. Is sugammadex economically viable for routine use. Curr Opin Anesthesiol 2012; 25(2): 17-20.
http://dx.doi.org/10.1097/aco.0b013e32834f012d

[43] Donati F. Sugammadex: an opportunity for more thinking or more cookbook medicine? Can J Anesth 2007; 54(9): 689-695.
http://dx.doi.org/10.1007/BF03026865

[44] Esteves S, Martins M, Barros F, Barros F, Canas M and Vitor P *et al*. Incidence of postoperative residual neuromuscular blockade in the postanaesthesia care unit: An observational multicentre study in Portugal. European Journal of Anaesthesiology 2013; 30(5): 243-249.
http://dx.doi.org/10.1097/EJA.0b013e32835dccd7

[45] Murphy GS. Residual neuromuscular blockade: incidence, assessment, and relevance in the postoperative period. Minerva Anestesiol 2006; 72: 97-109.

[46] Fortier LP, McKeen D, Turner K, de Médicis É, Warriner B and Jones PM, *et al*. The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade. Anesth Analg 2015 Apr 21 [Epub ahead of print].

[47] Brueckmann B, Sasaki N, Grobara P, Li MK, Woo T, de Bie J and Maktabi M *et al*. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth. 2015 May 2. pii: aev104. [Epub ahead of print].

[48] Churchill-Davidson HC and Christie TH. The diagnosis of neuromuscular block in man. Br J Anaesth 1959; 31: 290-301.
http://dx.doi.org/10.1093/bja/31.7.290

[49] Steward DJ. A simplified scoring system for the post-operative recovery room. Can Anaesth Soc J 1975; 22: 111-3.
http://dx.doi.org/10.1007/BF03004827

[50] Todd MM, Hindman BJ and King BJ. The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg 2014; 119(2): 323-31.
http://dx.doi.org/10.1213/ANE.0000000000000261

[51] Lee C and Katz RL. Muscle Relaxants 2006: a clinical and basic science update and commentary. Seminars in Anesthesia, Perioperative Medicine and Pain 2005; 24: 154-164.
http://dx.doi.org/10.1053/j.sane.2005.07.004

[52] Bulow K, Nielsen TG and Lund J. The effect of topical lignocaine on intubating conditions after propofol-alfentanil induction. Acta Anaesthesiol Scand 1996; 40(6): 752-6.
http://dx.doi.org/10.1111/j.1399-6576.1996.tb04523.x

[53] Cros AM, Lopez C, Kandel T and Sztark F. Determination of sevoflurane alveolar concentration for tracheal intubation with remifentanil, and no muscle relaxant. Anaesthesia 2000; 55(10): 965-9.
http://dx.doi.org/10.1046/j.1365-2044.2000.01538.x

[54] Donati F and Brull SJ. More Muscle Relaxation Does Not Necessarily Mean Better Surgeons or "The Problem of Muscle Relaxation in Surgery". Anesth Analg 2014; 119(5): 1019-1021.
http://dx.doi.org/10.1213/ANE.0000000000000429

[55] Madsen MV, Gätke MR, Springborg HH, Rosenberg J, Lund J and Istre O. Optimising abdominal space with deep neuromuscular blockade in gynaecologic laparoscopy--a randomised, blinded crossover study. Acta Anaesthesiol Scand. 2015; 59(4): 441-7.
http://dx.doi.org/10.1111/aas.12493

[56] Shirley Bassey. Never, never, never. 1973, United Artists.

Received on 08-05-2015 Accepted on 25-05-2015 Published on 30-06-2015

DOI: http://dx.doi.org/10.14205/2310-9394.2015.03.01.1