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Monitoring the Neuromuscular Junction: The Junction, Neuromuscular Blocking Agents and Technology

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- I have no conflicts

- Outline
- Neuromuscular Junction
- What should our student’s should know
- Muscle relaxants
- Reversal agents
- Current technologies in monitoring
- Newer technologies in monitoring

WE DO THIS FOR THE STUDENTS….

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Physiology of Neuromuscular Transmission

Nerve fiber termination and muscle innervation

Nerve impulses produce influx of calcium in nerve vesicle

Vesicles at nerve end release acetylcholine (ACH) into the synaptic cleft

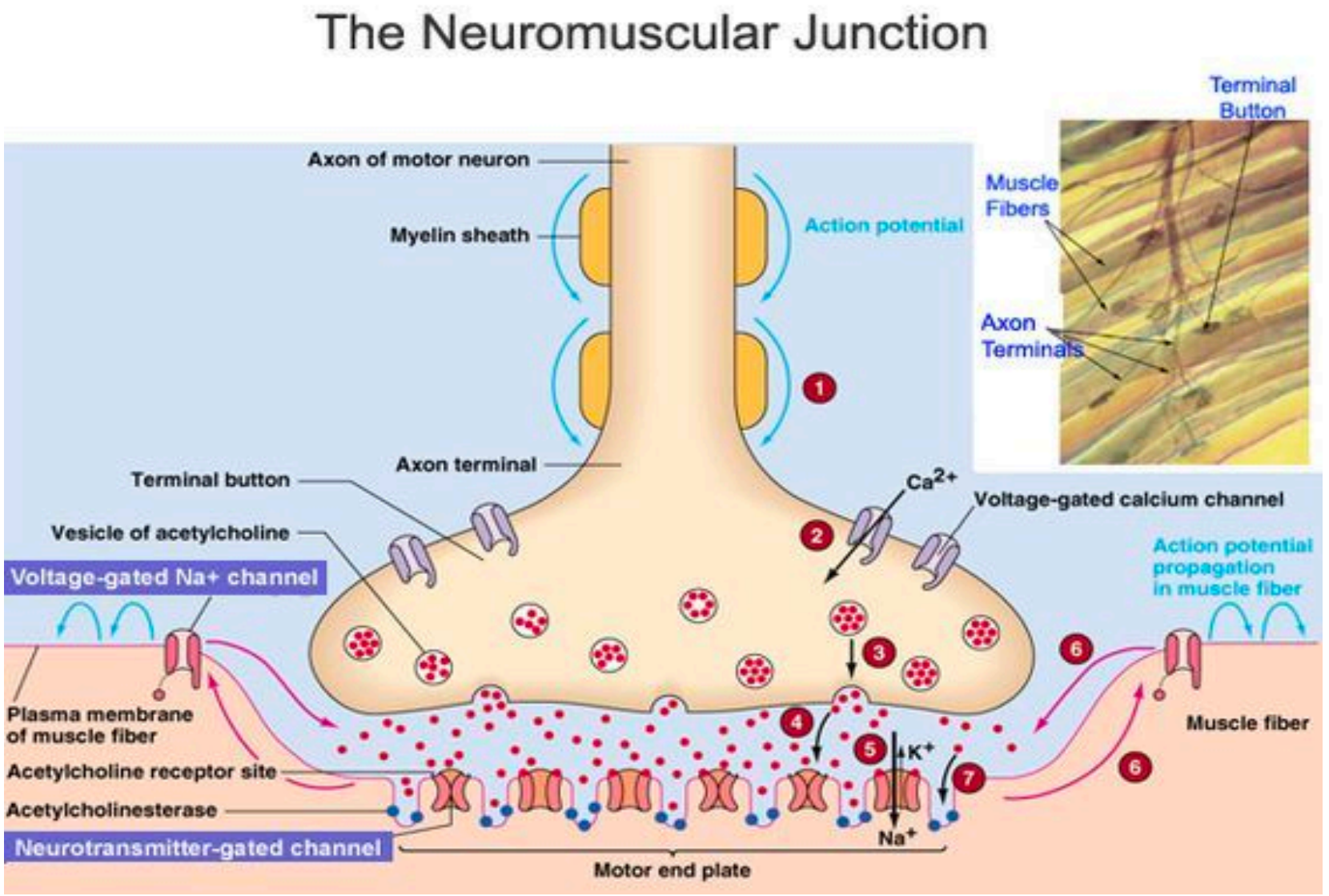
ACH diffuses across synaptic cleft to nicotinic receptor (cholinergic receptor) on post synaptic membrane

ACH binds to 2 alpha sub units on muscle

- Causes sodium channels to open

Influx of sodium and efflux of potassium occurs resulting in **depolarization** of muscle cells

- Causes paralysis of muscle



The Neuromuscular Junction

- There are two types of calcium channels
- DHPR act as voltage sensors and are activated by membrane depolarization which in turn activate ryanodine receptors
- Large amounts of calcium are released

- Shortly after releasing calcium the sarcoplasmic reticulum begins to reaccumulate calcium
- Once the calcium in the sarcoplasm has been lowered sufficiently, cross bridging between myosin and actin ceases and the skeletal muscle relaxes
- Failure of this calcium ion pump results in sustained contraction and marked increase in CO2 production

- Repolarization of the muscle membrane

- The return of the muscle membrane potential to its resting level is achieved by allowing chloride to enter the cell through voltage sensitive chloride channels.

- A bit of History:
- Natives of South America – Conquistadors
- Edward Bancroft –
- Sir Benjamin Brodie – small animal curare injection
- French physiologist – Claude Bernard (1813-1878) – frog leg
- 1942 – Wintersteiner and Dutcher
- 1942 – Harold Randall Griffith and Enid Johnson – first use?

Muscle Relaxants

- Non-depolarizers bind to one or both alpha subunits.
- When one or both alpha subunits are occupied the channel cannot open and depolarization can not occur.
- Muscle relaxation ends when the non-depolarizer diffuses away from the nicotinic acetylcholine receptor.
- Non-depolarizers are competitive antagonists.

- Depolarizing muscle relaxant (succinylcholine) consists of two molecules of acetylcholine bound together.
- Because succinylcholine is not hydrolyzed by acetylcholinesterase, the channel remains open for a longer period of time.
- Succinylcholine also causes inactivation of voltage gated sodium channels at the NMJ and increase in potassium permeability in the surrounding membrane.
- End result - failure of an action potential due to hyperpolarization.

- **DEPOLARIZERS**
  - Succinylcholine (Anectine®)
    - Mimics the action of acetylcholine
    - Acetylcholine receptor agonist

- **NON DEPOLARIZERS**
  - Rocuronium (Zemuron®)
  - Cistatracurium (Nimbex®)
  - Vecuronium (Norcuron®)
  - Atracurium (Tracrium®)
    - Blocks the action of acetylcholine

- SUCCINYLCHOLINE (Anectine®)
  - The only depolarizer in clinical practice
  - Dose : 1-1.5mg/kg
  - Rapid onset – 60 seconds
  - Short duration of action - up to 10 minutes
  - Causes fasciculation of muscles
  - Adverse reactions – what should the student know?
  - Metabolism : plasma cholinesterase

- Diffuse from the neuromuscular junction
- Hydrolyzed in plasma and liver by pseudocholinesterase
  - Nonspecific cholinesterase
  - Plasma cholinesterase
  - butyrylcholinesterase

- ROCURONIUM (Zemuron®)
  - Classified as an aminosteroid neuromuscular blocking agent
  - Dose: 0.6-1.2mg/kg
  - Onset 1.5 -3 min
  - Duration of action 20-35 min
  - Lacks potency
  - Resembles onset of succinylcholine with increased dose
  - With renal disease, may have longer duration of action

- CISATRACURIUM (Nimbex®)
  - Classified as a benzylisoquinolinium neuromuscular blocking agent
  - Dose 0.15-0.2 mg/kg
  - Onset of action - 3-5 minutes
  - Duration of action - 20-35 minutes
  - Undergoes Hoffman elimination and ester hydrolysis
  - Great for patients with significant renal disease or renal failure

- ATRACURIUM (Tracrium®)
  - Classified as a benzylisoquinolinium neuromuscular blocking agent
  - Dose – 0.4-0.5mg/kg
  - Onset – 2 minutes
  - Duration of action– 35-70 minutes
  - Undergoes Hoffmann elimination and ester hydrolysis

Reversal of neuromuscular blocking agents

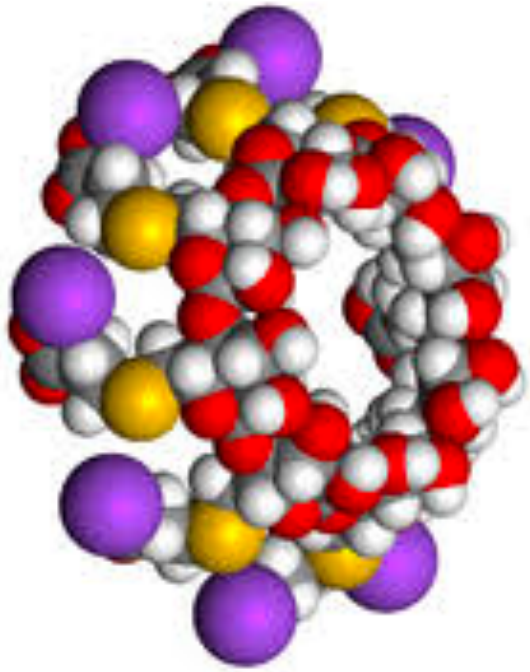
Neostigmine
Physostigmine
Edrophonium
Glycopyrrolate
Atropine
Sugammadex

- CHOLINESTERASE INHIBITORS
  - Blocks action of acetylcholinesterase
  - More acetylcholine present for muscle contraction
  - Neostigmine – quaternary amine
  - Physostigmine – tertiary amine
  - Edrophonium – quaternary amine

- STUDENT QUESTION - Why do I need an anticholinergic?
- Atropine
- Glycopyrrolate

Sugammadex – changing practice

- Bridion® - novel cyclodextrin
- Selective relaxant binding agent (SRBA)
- First produced in 1999
- Revolutionized muscle relaxant reversal
- Actively binds to rocuronium and vecuronium
- Forms a complex – which inactivates the drug



- https://www.youtube.com/watch?v=BJhuA8Dlp50

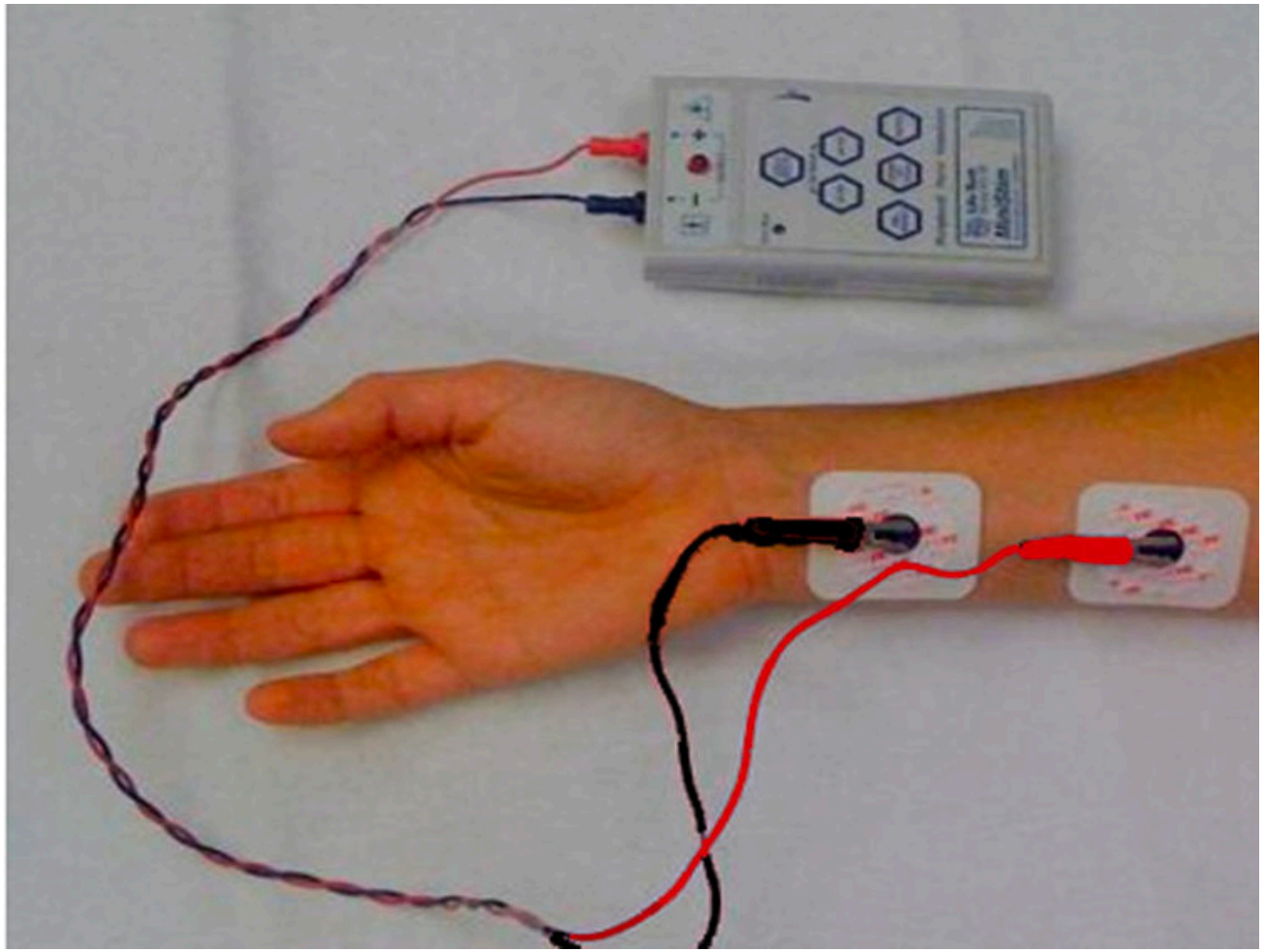
- Sugammadex
- Dose based on subjective measurement

Level of NMB with rocuronium or vecuronium	Dose of BRIDION	Example dose of BRIDION for a patient weighing 80 kg
If spontaneous recovery has reached **the reappearance of the second twitch (T_2)** in response to TOF stimulation	2 mg/kg	160 mg (1.6mL)
If spontaneous recovery of the twitch response has **reached 1-2 posttetanic counts (PTCs), no twitch responses to TOF**	4 mg/kg	320 mg (3.2 mL)

Technology

TRAIN-OF-FOUR

- Subjective monitoring
- Train of Four Monitoring – a quick review
- Single twitch – potency of NMBA
- Train of four – fade
  - Train-of-four count (TOFC)
  - 1 - >95
  - 2 – 85-90
  - 3 – 80-85
  - 4 – 70-75



- Train-of-Four
- Tetanus – sustained contraction
- Post-tetanic potentiation – useful during deep levels of blockade
- STUDENT QUESTION – Think about what happens with tetany, as a practitioner, what may we potentially do based on this?
- Double Burst – developed because assessment of two stimuli may be more accurate
- Fade – difficulty in assessment

- OBJECTIVE MONITORING
- Acceleromyography
- Electromyography
- Kinemyography

Acceleromyography

- Has been in use since ~1998
- Adductor pollici
- Newton's second law
- Position must stay the same – thumb free
- Calibration prior to NMBA administration

- Electromyography
- Skin stimulation electrodes, generation of an action potential
- Does not require unrestriction of the hand
- Leads placed over the ulnar nerve
  - Adductor pollici
  - Abdcutor digiti minimi
  - First dorsal interosseus

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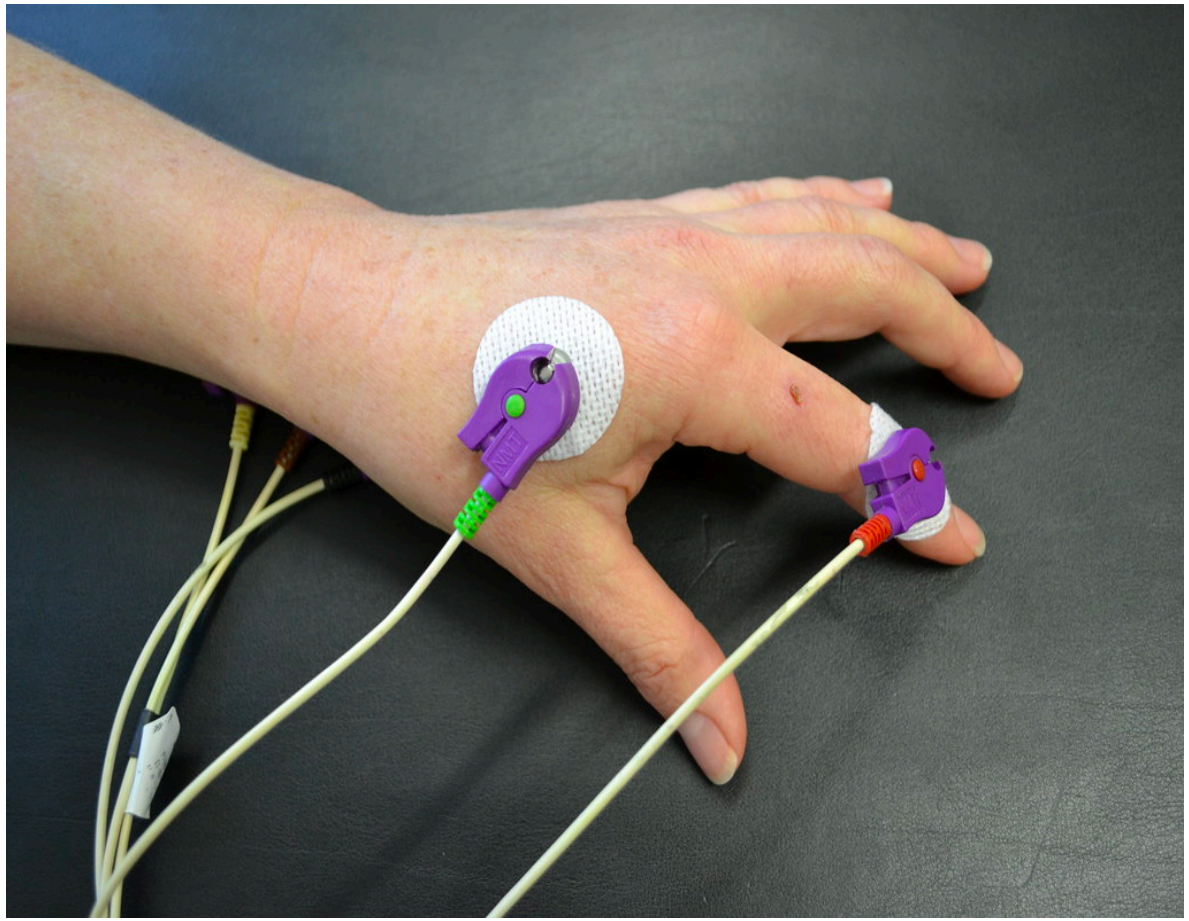
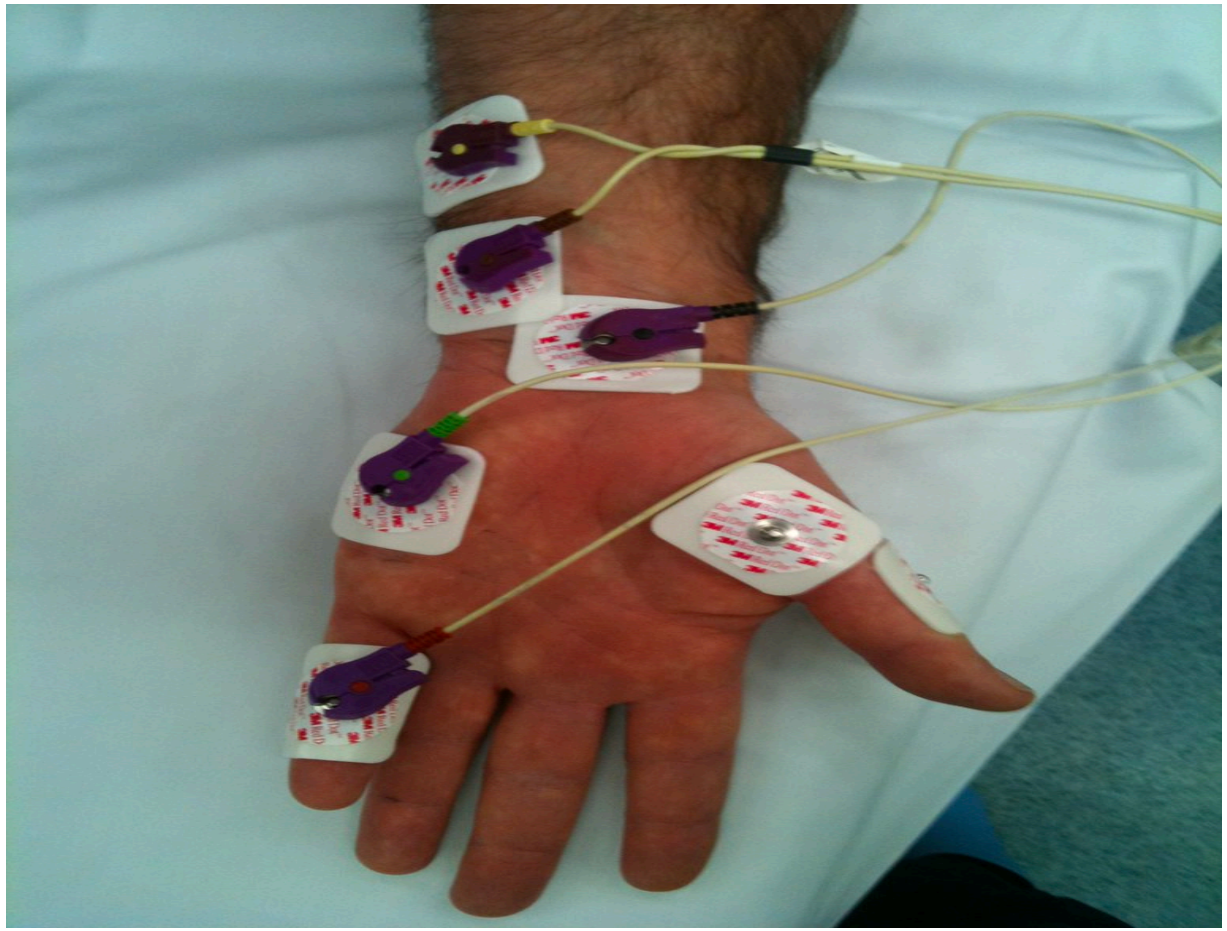
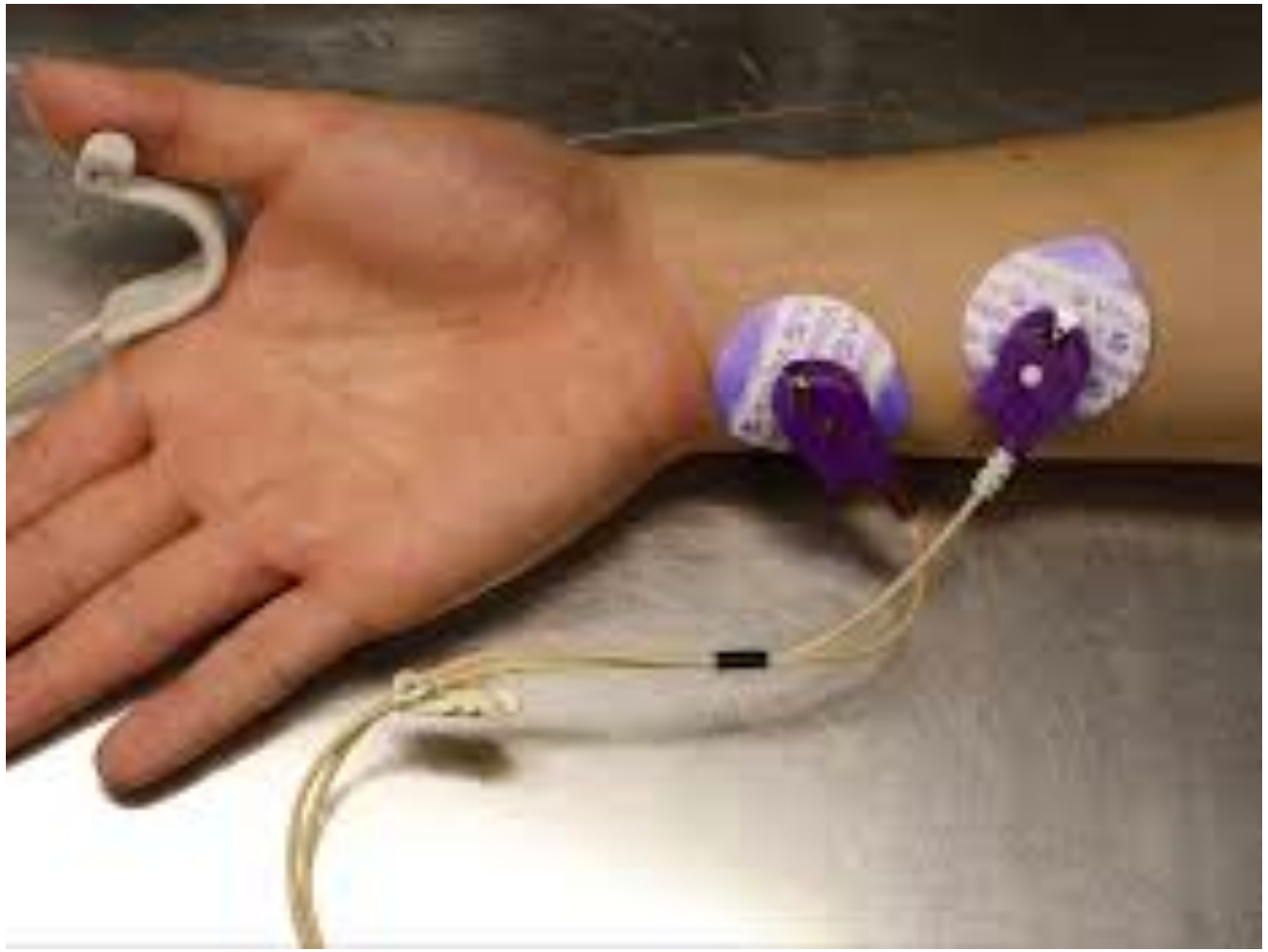




Kinemyography

- Kinemyography
- Electrical stimulation generated from distortion of stimulator
- Results not interchangeable with other modalities
- Similar limitations as the AMG
- Easy to use, more reliable than subjective methods



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Current Status of Neuromuscular Reversal and Monitoring

Challenges and Opportunities

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Implementation of Acceleromyography to Increase Use of Quantitative Neuromuscular Blockade Monitoring: A Quality Improvement Project

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Intraoperative Acceleromyography Monitoring Reduces Symptoms of Muscle Weakness and Improves Quality of Recovery in the Early Postoperative Period

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