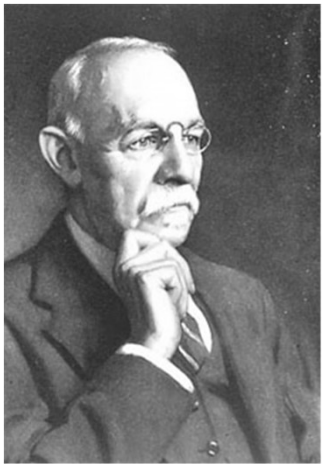
LOCAL ANAESTHETICS: update

Juri Karjagin
University of Tartu
Tartu University Hospital

The advent of anaesthesia has made it so that any idiot can become a surgeon.



William Stewart Halsted, 1852-1922

EJA

Eur J Anaesthesiol 2014; **31**:575–585

REVIEW

Local anaesthetics: 10 essentials

Philipp Lirk, Susanne Picardi and Markus W. Hollmann

Some history…

- 5000 year ago cocaine was used as painkiller
- 1563 Cobo first described in details analgesic effect he experienced

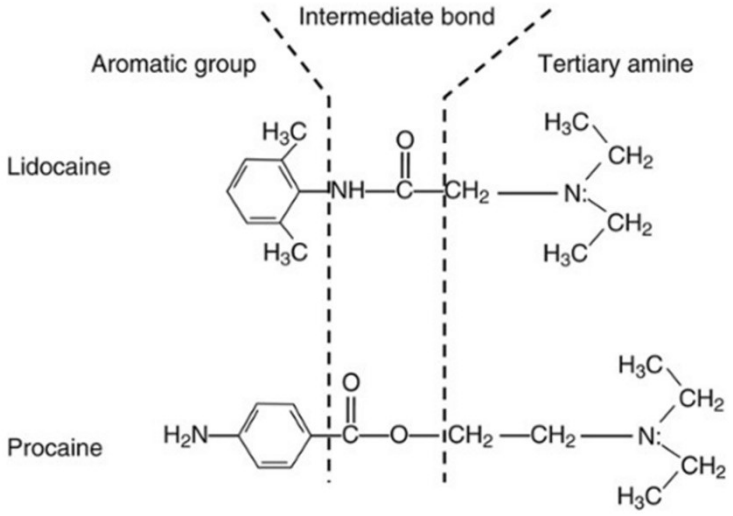
- 1880 B. Anrep recomended cocaine for surgical anaesthesia
- 11.09.1884 Karl Koller first local anaesthesia in eye surgery

Synthetic …caines

- 1904 Alfred Einhorn synthetised procaine (novocaine) and 1905 Heinrich Braun used it
- 1925 Otto Eisleib – tetracaine
- 1943 Nils Löfgren and Bengt Lundquist – lidocaine
- 1949 HC Marks and MI Rubin – chloroprocaine
- 1957 Bo Af Ekenstam – mepi- and bupivacaine, ropivacaine
- 1969 Löfgren and Tegner – prilocaine
- 1972 Adams etidocaine and Winther articaine

BASIC

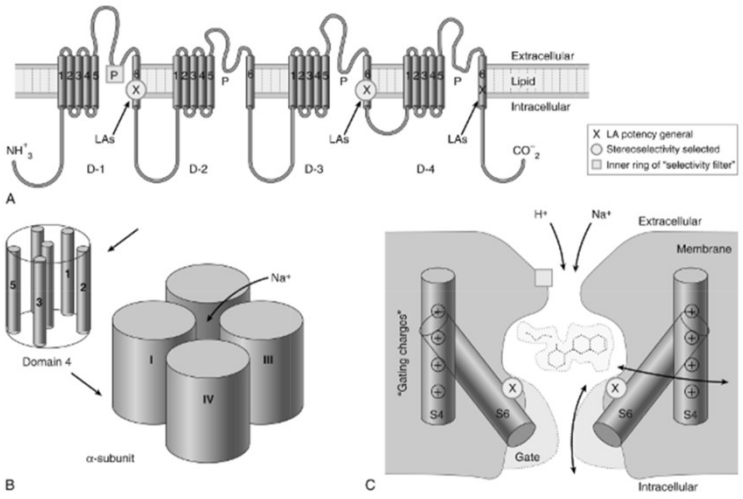
Chemical structure



„I“ is important

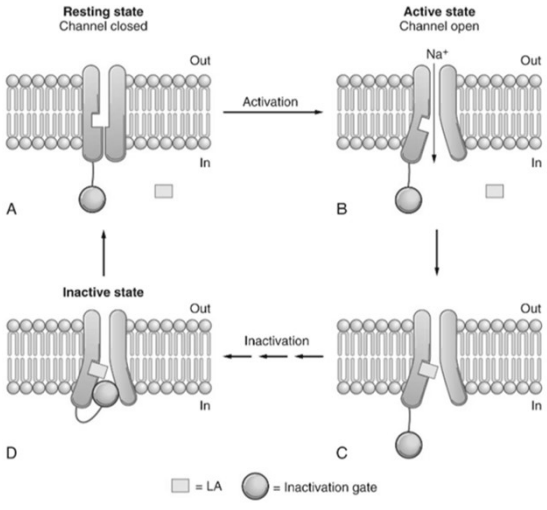
Amides	Esters
Bupivacaine	Benzocaine
Etidocaine	Chloroprocaine
Levobupivacaine	Cocaine
Lidocaine	Procaine
Mepivacaine	Tetracaine
Prilocaine	
Ropivacaine	

Main target - VGSC



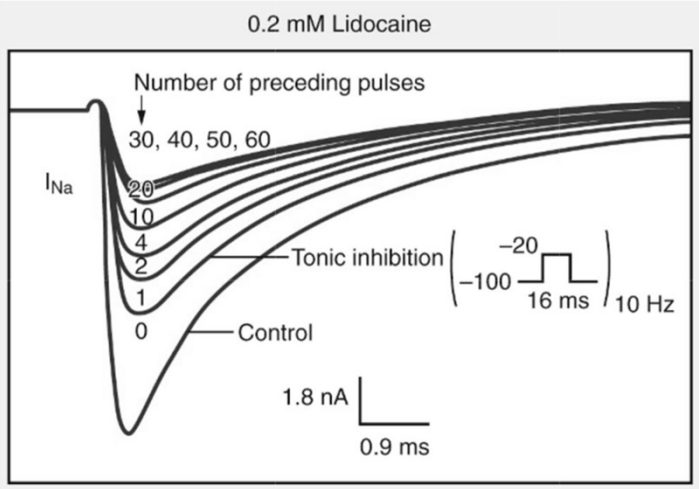
Miller's Anesthesia 8th ed 2014

Main target = VGSC

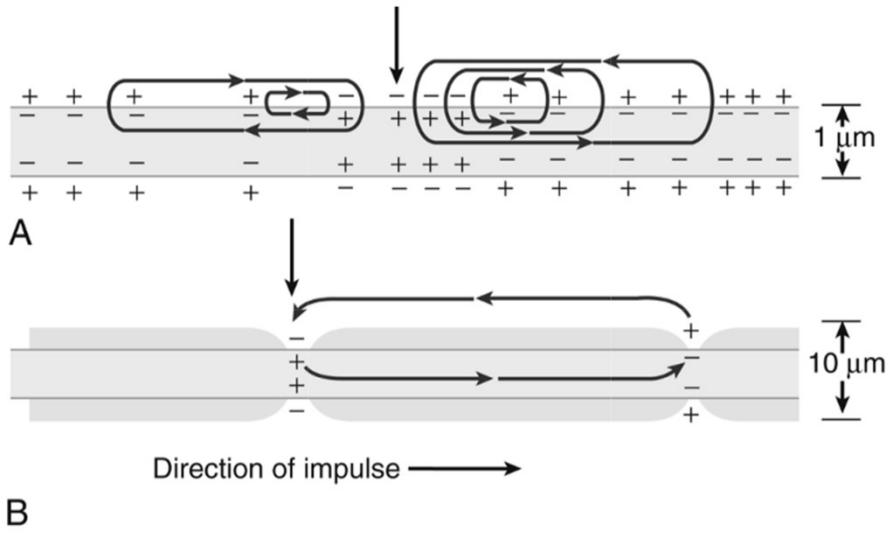


Miller's Anesthesia 8th ed 2014

Use-dependent = phasic block

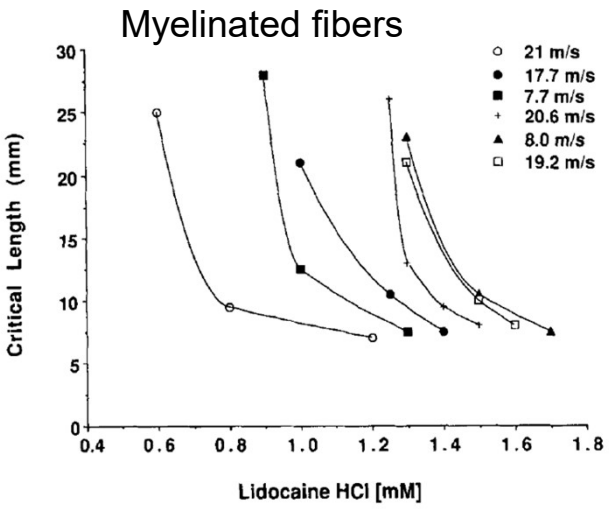


Miller's Anesthesia 8th ed 2014



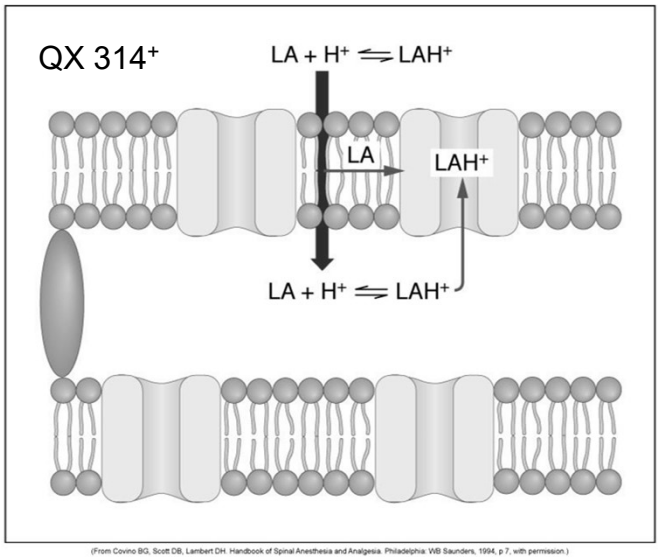
Miller's Anesthesia 8th ed 2014

How much should be blocked?



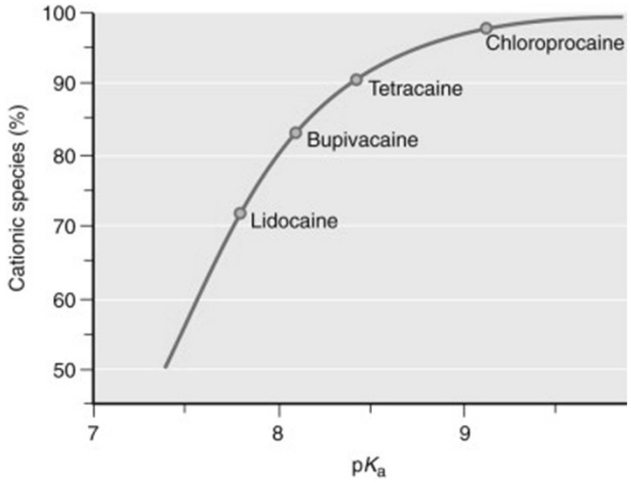
pH (Acidity) is important

Weak bases
HCl salts
Mostly ionized



(From Covino BG, Scott DB, Lambert DH. Handbook of Spinal Anesthesia and Analgesia. Philadelphia: WB Saunders, 1994, p 7, with permission.)

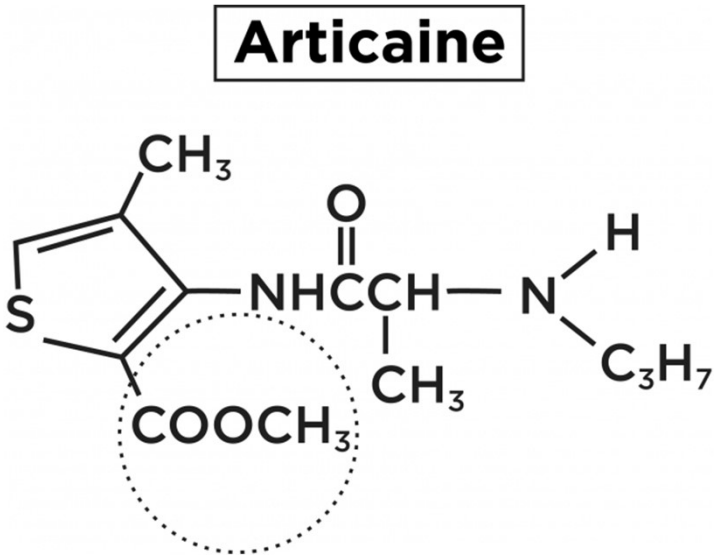
pH is important



Miller's Anesthesia 7th ed 2009

Bond is important

- Esters metabolised in blood stream by pseudocholinesterase
  - no pseudocholinesterase in CSF >> rate of absorption
- Amides
  - metabolised in liver by cytP450
    - CYP1A2 (lido, ropi)
    - CYP2D6 (lido)
    - CYP2E1 (ropi)
    - CYP3A4 (lido, ropi, bupi)
  - high-extraction drugs
- Articaine…



Bond is important

- Esters metabolised in blood stream by pseudocholinesterase
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- Amides
  - high-extraction drugs
  - metabolised in liver by cytP450
    - CYP1A2 (lido, ropi)
    - CYP2D6 (lido)
    - CYP2E1 (ropi)
    - CYP3A4 (lido, ropi, bupi)
- Articaine a little bit of both

free Concentration / protein binding

- Duration = binding

Table 1 Physicochemical properties of local anaesthetics

Substance	pKa	LAb (%)	O/B coeff	PB (%)	MW (Da)	EAC
Lidocaine	7.9	25	2.4	64	234	1
Mepivacaine	7.6	39	21	77	246	1
Bupivacaine	8.1	15	346	95	288	0.25
Ropivacaine	8.1	15	115	94	274	0.5
Prilocaine	7.9	24	25	55	220	1
Procaine	8.9	3	1.7	6	236	2
Articaine	7.8	28	17	70	321	1

- Systemic toxicity = free fraction and affinity to receptor

B ond – metabolism pathhway and metabolites

A cidity - more acidic enviroment, less effect

S sodium channel main tärget, not the only one

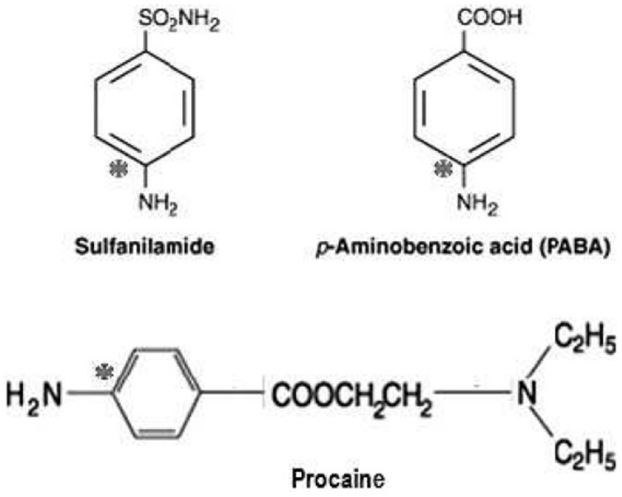
I is omportant too

C free Concentration and protein binding

ALLERGY

Allergy- I type reactions

- Incidence during anaesthesia: 1:677 – 1:34 0000
- LA 0.33% of that
- Adverse reactions to LA
  - reactions to injection (vagal syncopes)
  - reactions to adrenaliine (palpitations, headaches etc)
  - allergic reactions
    - LA and metabolites
    - Conservation additives: methyl-paraben, sulfite
- Esters are allergens



Becker DE & Reed KL Anesth Prog 2012

Allergy

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  - allergic reactions
    - LA and metabolites
    - Conservaation additives: methyl-paraben, sulfite
- Esters are allergens – NO, metabolites YES
- Sulfite – be aware persons who allegic to fresh fruits and vegetables

No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre

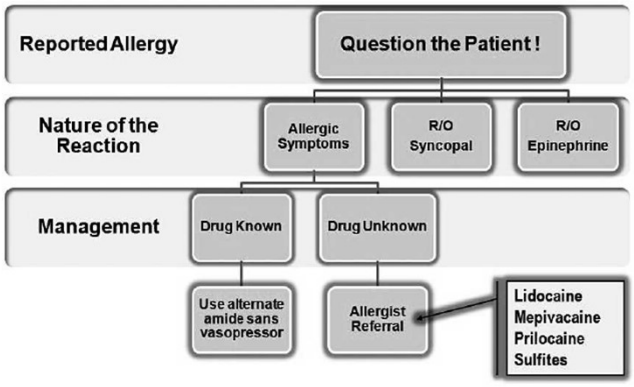
A. D. Kvisselgaard, M. Krøigaard, H. F. Mosbech and L. H. Garvey

Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup,Denmark

- 2004 – 2013 162 patients claimed to be allergic to LA
- NO ONE really was
- 52 were allergic to other compounds, like chlorhexedine, cefuroxime, patent blue

- At the same period app. 1.5 mln patients exposed to LA

Patient claims allergy



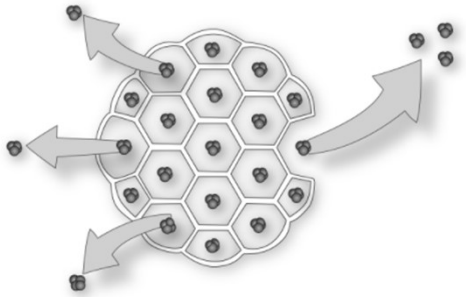
Becker DE & Reed KL Anesth Prog 2012

SLOW-RELEASE

Slow-release bupivacaine

- Liposomal bupivacaine
- SABER® bupivacaine

Liposomal bupivacaine (EXPAREL)



Cochrane Database of Systematic Reviews

Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain

Review Intervention

Thomas W Hamilton ✉, Vassilis Athanassoglou, Stephen Mellon, Louise H Strickland, Marialena Trivella, David Murray, Hemant G Pandit

First published: 1 February 2017

Authors' conclusions

Liposomal bupivacaine at the surgical site does appear to reduce postoperative pain compared to placebo, however, at present the limited evidence does not demonstrate superiority to bupivacaine hydrochloride. There were no reported drug-related serious adverse events and no study withdrawals due to drug-related adverse events. Overall due to the low quality and volume of evidence our confidence in the effect estimate is limited and the true effect may be substantially different from our estimate.

Cochrane Database of Systematic Reviews

Liposomal bupivacaine peripheral nerve block for the management of postoperative pain

Review Intervention

Thomas W Hamilton ✉, Vassilis Athanassoglou, Marialena Trivella, Louise H Strickland, Stephen Mellon, David Murray, Hemant G Pandit

First published: 25 August 2016

Authors' conclusions

A lack of evidence has prevented an assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block. At present there is a lack of data to support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

SABER

- **SABER** = **S**ucrose **a**cetate iso**b**utyrate **e**xtended **r**elease
- Formulation have to be instilled into the open wound
- One published study
- Some small studies reported at different meetings
- Better than placebo
- ??? than bupivacaine HCl

COST????

SYSTEMIC USE

Lidocaine

Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis†

S. Weibel[1,*], J. Jokinen[1], N. L. Pace[2], A. Schnabel[1], M. W. Hollmann[3], K. Hahnenkamp[4], L. H. J. Eberhart[5], D. M. Poepping[6], A. Afshari[7] and P. Kranke[1]

- 45 studies 2402 patients
- 1395 lidocaine and 1407 placebo or nothing (2 studies)
- Perioperative lidocaine regimens were quite diferent
  - Bolus 1-3 mg/kg
  - Infusion rate
  - Duration: operation, postop
- Open abdominal, laparoscopic abdominal, other surgeries

Weibel S et al. BJA 2016

Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis†

S. Weibel[1,*], J. Jokinen[1], N. L. Pace[2], A. Schnabel[1], M. W. Hollmann[3], K. Hahnenkamp[4], L. H. J. Eberhart[5], D. M. Poepping[6], A. Afshari[7] and P. Kranke[1]

Table 2 Subgroup analyses – comparison: lidocaine vs control (placebo/untreated). Subgroups were built for patients undergoing either open abdominal, laparoscopic abdominal, and other surgeries. Effect sizes were reported as MD or RR with 95% CI. Effect sizes <0 for continuous data (MD) and <1 for dichotomous data (RR) indicate 'favour of' lidocaine treatment

Subgroup	Pain 'early', (VAS 0–10 cm)	Opioid requirements, 'post-OP' (MEQ, mg)	PON(V) 'late', 0–24 h, −48 h, −72 h
Open abdominal surgery	−0.72 [−0.96, −0.47]	−3.26 [−4.80, −1.71]	0.87 [0.67, 1.13]
Laparoscopic abdominal surgery	−1.14 [−1.51, −0.78]	−7.40 [−11.41, −3.38]	0.73 [0.54, 0.98]
Other surgery	−0.30 [−0.89, 0.28]	−7.28 [−12.91, −1.65]	0.83 [0.57, 1.22]
Overall	−0.84 [−1.10, −0.59]	−5.36 [−7.12, −3.59]	0.82 [0.70, 0.97]

Trials are small
Heterogeneity was high

Laparoscopic surgery
1.5 mg/kg bolus
2 mg/kg/t during operation

Weibel S et al. BJA 2016

CANCER and LA

NARRATIVE REVIEW ARTICLE

CME Perioperative Anesthesia Care and Tumor Progression

Mir W. Sekandarzad, FANZCA, FFPMANZCA, DESA,* André A.J. van Zundert, MD, PhD, FRCA, EDRA, FANZCA,* Philipp B. Lirk, MD, PhD,† Chris W. Doornebal, MD,† and Markus W. Hollmann, MD, PhD, DEAA†

- Inhibition of TNF-α induced Src protooncogene activation and intercellular adhesion >> affect migration
- Inhibition of epidermal growth factor receptors
- Antiproliferation of mesenchymal stem cells
- Block of α-subunit of VGSC >> affect invasiveness and growth activity
- Demethylating properties >> growth inhibition
- Lidocaine and bupivacaine induce apoptosis in breast cancer cells

Sekandarzad MW et al. A&A May 2017

Table 2. Regional Anesthesia Outcomes

Study	Year	Type of Study	Total Number of Patients RA/GA	Surgery	End Points	Hazard Ratio	95% CI	Outcome
Cakmakkaya[70]	2014	SR	392/354	Colon, major abdominal, prostate	OS	1.02	0.78–1.34	NEG
					PFS	0.88	0.56–1.38	NEG
					TTP	1.5	1.00–2.25	NEG
Weng[68]	2015	SR	15160/36460	Prostate, laryngeal, ovarian, colorectal, hypopharyngeal, abdominal, breast, hepatocellular	OS	0.853	0.741–0.981	POS
					RFS	0.846	0.718–0.998	POS
Sun[69]	2015	SR	16618/37923	Prostate, laryngeal, ovarian, colorectal, melanoma, abdominal, breast, hepatocellular	OS	0.84	0.75–0.94	POS
					RFS	0.91	0.70–1.18	NEG
Chen[72]	2013	SR	11575/34826	Colon, rectal, ovarian, abdominal, breast, cervical, hepatocellular	OS	0.84	0.74–0.96	POS
					RFS	0.88	0.64–1.22	NEG
Pei[71]	2014	SR	1553/1903	Breast, prostate, colon, colorectal, gastroesophageal	RRa or MET	0.88	0.73–1.06	NEG
Exadaktylos[42]	2006	RETRO	50/79	Breast	RFS	0.21	0.06–0.71	POS
Tsigonis[55]	2016	RETRO	646/461	Breast	OS	0.81	0.59–1.10	NEG
					DFS	0.91	0.55–1.76	NEG
					LR	1.73	0.83–3.63	NEG
Scavonetto[45]	2014	RETRO	1642/1642	Prostate	SP	2.81	1.31–6.05	POS
Churruca[60]	2012	RETRO	Total 2173	Prostate	CR	1.4	1.1–1.9	NEG
Bakr[30]	2008	RETRO	102/123	Prostate	BFS	0.43	0.22–0.83	POS
Wuethrich[34]	2010	RETRO	103/158	Prostate	CPFS	0.45	0.27–0.75	POS
Wuethrich[61]	2013	RETRO	67/81	Prostate	OS	1.17	0.63–2.17	NEG
Forget[59]	2011	RETRO	578/533	Prostate	BFS	0.84	0.52–1.17	NEG
Koonce[64]	2014	RETRO	213/406	Breast	CR	N/A	N/A	NEG
Tsui[47]	2010	RCT	49/50	Prostate	BFS	1.33	0.64–2.77	NEG
Rotas[32]	2014	OBS	3047/1725	Prostate	OS	0.9	0.51–1.6	NEG
Cummings[37]	2012	OBS	9278/40377	Colorectal	OS	0.91	0.87–0.94	POS
Cummings[38]	2014	OBS	766/1979	Gastric	M	0.93	0.84–1.03	NEG
Myles[65]	2011	RCT	230/216	Abdominal, pelvic	OS	0.96	0.79–1.17	NEG
Christopherson[43]	2008	PRO	85/92	Colon	OS	0.22	0.07–0.69	POS
Holler[58]	2013	RETRO	442/307	Colorectal	OS	0.73	N/A, $P < .02$	POS
Gupta[36]	2011	RETRO	562/93	Colon	OS	0.82	0.30–2.19	NEG
				Rectal	OS	0.45	0.22–0.90	POS
Gottschalk[62]	2010	RETRO	256/253	Colon	RFS	0.82	0.49–1.35	NEG
Day[63]	2012	RETRO	251/173	Colorectal	OS	N/A	N/A, $P = .622$	NEG
Merquiol[44]	2013	RETRO	111/160	Head and neck	OS	0.61	0.39–0.96	POS
					CFS	0.49	0.25–0.96	POS
Schlagenhauf[66]	2000	RETRO	2185/2136	Melanoma	RR of death	N/A, HR for GA 1.46	1.21–1.76	POS
Gottschalk[39]	2012	RETRO	52/221	Melanoma/LND	OS	*	N/A, $P = .087$	EQUI
Lin[40]	2011	RETRO	106/37	Ovarian	SuvR	1.214	1.075–1.431	POS
Capmas[28]	2012	RETRO	47/47	Ovarian	OS	1.25	0.39–4.04	NEG
De Oliveira[35]	2011	RETRO	55/127	Gynecology	TTR	0.37	0.19–0.73	POS
Sprung[53]	2014	RETRO	486/486	Prostate	CR	0.79	0.6–1.04	NEG
Ehdaie[48]	2014	RETRO	264/665	Prostate	BR	1.1	0.7–1.74	NEG
Tseng[46]	2014	RETRO	1166/798	Prostate	BR	1.1	085-1.42	NEG
Hiller[33]	2014	RETRO	97/43	Gastro-esophageal	OS	0.42	0.21–0.83	POS
					CR	0.33	0.17–0.63	POS
Heinrich[50]	2014	RETRO	118/35	Esophageal	LR	3.62	1.58–8.32	NEG
Ismail[56]	2010	RETRO	63/69	Cervical	LR or SysR	0.95	0.54–1.67	NEG
Binucak[54]	2013	RETRO	69/63)	Intra-abdominal	RFS	1.3	0.8–2.0	NEG
Lai[31]	2012	RETRO	62/117	Hepatic	RFS	4.31	2.24–8.29	NEG
					OS	1.26	0.81–1.97	NEG
Lacassie[57]	2013	OBS	37/43	Ovarian	OS	0.74	0.36–1.49	NEG

Abbreviations: BFS, biochemical recurrence free survival; BR, biochemical recurrence; CFS, cancer-free survival; CPFS, clinical progression free survival; CR, cancer recurrence; DFS, disease-free survival; EQUI, equivocal outcome; GA, general anesthesia; LR, local recurrence; LND, lymph node dissection; MET, metastasis; MR, mortality rate; NEG, negative outcome; OBS, observational; OS, overall survival; POS, positive outcome; PRO, prospective study; RA, regional anesthesia; RCT, randomized controlled trial; RETRO, retrospective study; RFS, recurrence-free survival; RR, relative risk; RRa, recurrence rate; SP, systemic progression; SR, systematic review; Sys R, systemic recurrence; TRR, tumor recurrence risk; TTP, time to tumor progression.

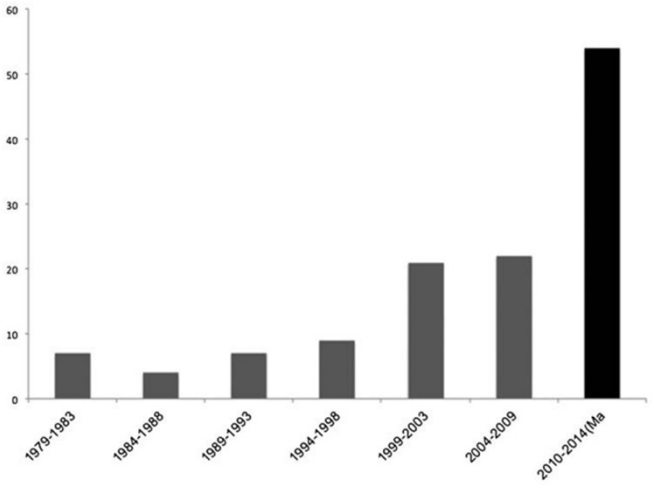
*Trend toward longer survival in spinal anesthesia group.

Sekandarzad MW et al. A&A May 2017

LAST

Local Anaesthetic Systemic Toxicity

LAST: 1979-2014



Vasques F et al. RAPM 2015
Di Gregorio G et al. RAPM 2010

Incidence of LAST

- Peripheral nerve blocks
  - At the end of 20th century, 7-20 per 10 000 blocks
  - Nowadays, 2.0 – 2.8 per 10 000 blocks
- Epidurals
  - Before 1981 100 per 10 000 epidurals (introduction of test dose and incremental injection)
  - Nowadays, 0.7-1.8 per 10 000 epidurals
- Recent changes
  - Local infiltration techniques
  - Large volume blocks: TAP, PECS
  - Often performed in anaesthetised patients
  - 30% is from other specialities

Mnemonics (greatest to least)

- BICEPSS
- B= blood/tracheal
- I= intercostal
- C= caudal and para “cervical”
- E = epidural
- P= perivascular brachial plexus
- S= sciatic/spinal
- S= subcutaneous

Prevention

- Using drugs with lower toxicity potential
  - Bupivacaine > ropi/levo > lidocaine
- Dosage reductions
- Inject slowly
  - 3-5 ml >> pause 15-30 s >> 3-5 ml
- Aspirate before each injection (2% false-negative)
- Using of markers
  - Adrenaline, but up to 87% false-positive
  - Fentanyl (sedation)
  - LA
- Ultrasound guidance (USG)

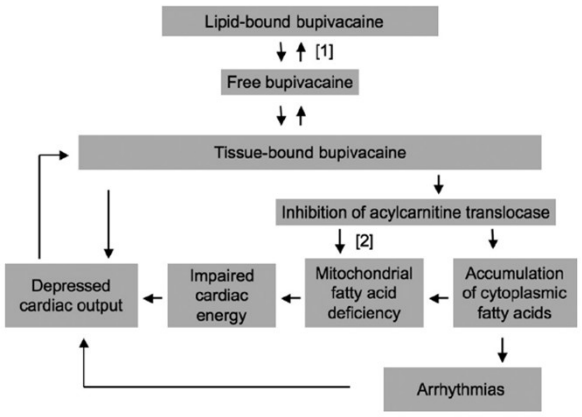
Second ASRA assessment of USG

- US lowers the risk of unitended vascular puncture (LOE Ia)
- Registry data strongly support the statement that USG reduces the incidence of LAST (LOE III)
- USG does NOT completely eliminate the risk of LAST, therefore practioners should remain vigilant…

Neal JM et al. RAPM 2016

Lipid emulsion

2006 Rosenblatt first succesful resuscitation case report in human



Drassner K RAPM 2010

Summary

- Local anaesthteics main target is VGSC
- Important for effect are
  - tissue pH
  - protein binding / free concentration
  - Chemical structure
- Systemic toxicity
  - is not only anaesthesiologists problem
  - absorption is becoming more often as a reason
  - USG can reduce dose and inadverent vessel puncture
  - Lipid emulsioon
- Allergy is uncommon for amide type
- Systemic use of lidocaine in laparoscopic surgery
- LA against cancer