

Kan anestesiteknik påverka utfall efter cancerkirurgi?

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3. Effekter av lokalanestestika utöver själva blockaden



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CA COST Action CA15204
**European Platform for Outcomes Research
into Perioperative Interventions during
Surgery for Cancer**

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Chair of the Action:
Prof. Donal Buggy,
Dublin, Ireland



COST Action 15204



The screenshot shows the 'Parties' section of the e-COST website for COST Action CA15204. The page has a header with the e-COST logo and navigation links: Home, COST Actions, COST Association, CA15204, and Parties.

CA COST Action CA15204

Parties

Action details

MoU	Draft: OC-2015
CSO Approval date	26/07/2015
Start of Action	
End of Action	

Participants (14 confirmed)

Country	Name	Title	Organization	Email	Status
Sweden	Dr Mats ENLUND	MC Member	Uppsala University and the County Council of Västmanland/Centre for Clinical Research, Uppsala University, Entrance 29, Central Hospital SE-721 89 Västerås Sweden	mats.enlund@ltv.se	Confirmed
Greece	▶ Greece				Confirmed
Ireland	▶ Ireland				Confirmed
Italy	▶ Italy				Confirmed
Lithuania	▶ Lithuania				Confirmed
Montenegro	▶ Montenegro				Confirmed
Netherlands	▶ Netherlands				Confirmed
Romania	▶ Romania				Confirmed
Spain	▶ Spain				Confirmed
Sweden	▶ Sweden				Confirmed
Switzerland	▶ Switzerland				Confirmed
United Kingdom	▶ United Kingdom				Confirmed
Total: 14					

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Narkosmedel och cancerkirurgi?

Propofol-sövda råttor har lägre incidens av recidiv och metastasering i cancer-modeller, och de lever längre jämfört med råttor som fått inhalationsanestetika.

Gilliland H, et al. Anesth Analg 1997;85:1394-8

Lundy J, et al. Cancer 1978;41:827-30

Shapiro J, et al. J Clin Invest 1981;68:678-85

Kotani N, et al. Anesthesiology 1998;89:1125-32

Moudgil G, Singal D. Can J Anesth 1997;44:90-4

Schneemilch CE, Bank U. Anaesthesiol Reanim 2001;26:4-10

Mammoto T, et al. Cancer Lett 2002;184:165-70

Melamed R, et al. Anesth Analg 2003;97:1331-9

Schneemilch CE, et al. J Clin Anesth 2005;17:517-27

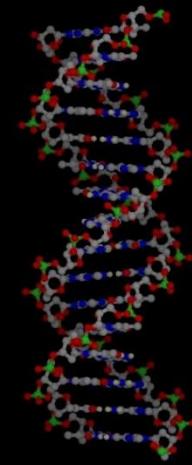
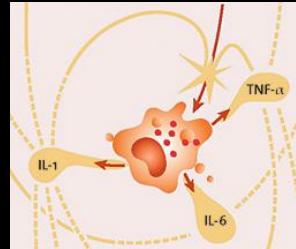
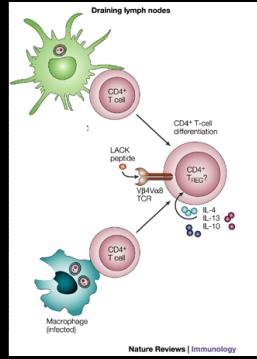
Kushida A, et al. Immunopharmacol Immunotoxicol 2007;29:477-86

Ke J, et al. Anaesth Intensive Care 2008;36:74-8

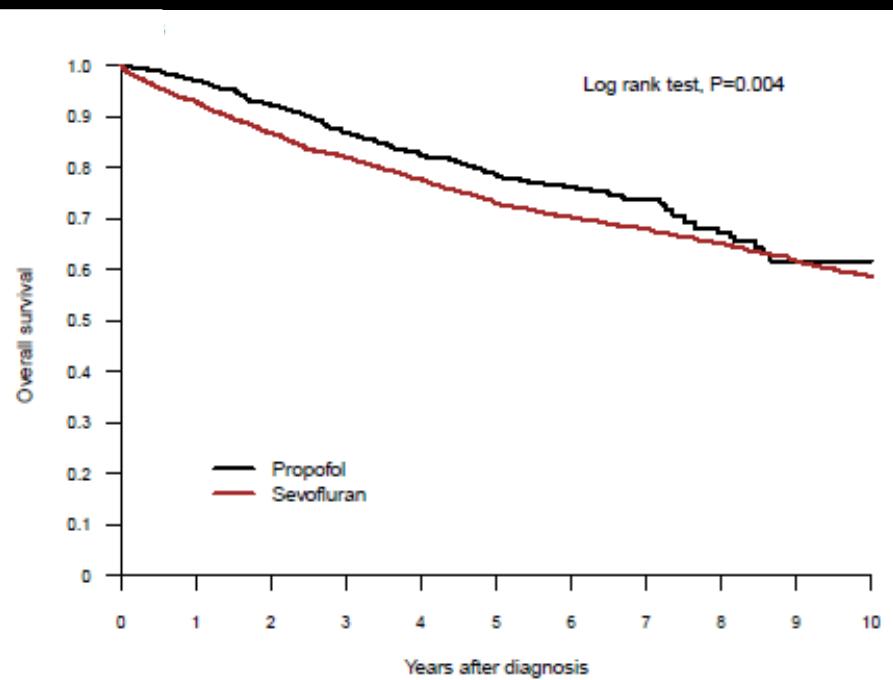
Narkosmedel och cancerkirurgi?

Det finns åtminstone tre tänkbara mekanismer

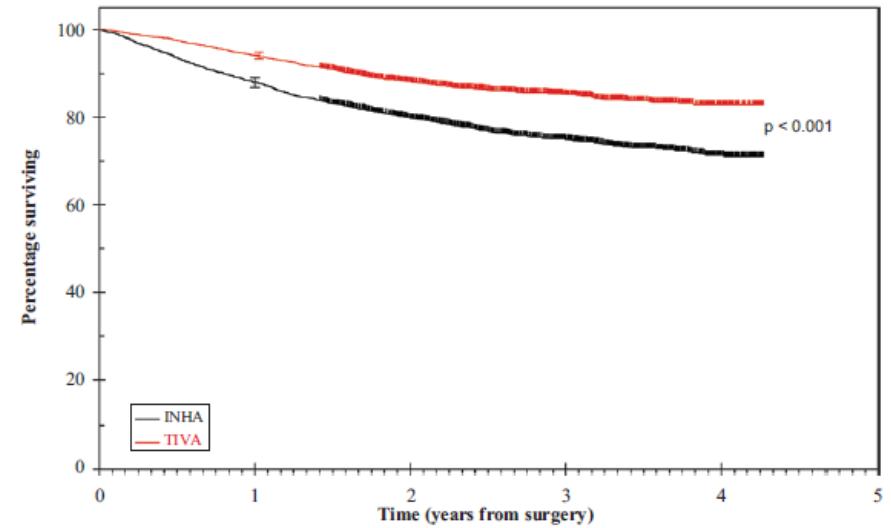
- Olika effekter på immunsystemet
- Olika effekter på DNA
- Olika effekter på hypoxia-inducible factor



Retrospektiva human-data



Enlund M, et al.
Ups J Med Sci 2014;119:251-61



Wigmore TJ, et al.
Anesthesiology 2016;124:69-79



Fler retrospektiva studier

- 2016, Lee JH, Korean J Anesthesiol, breast cancer, n = 325.
- 2017, Jun IJ, Sci Rep, esophageal cancer, n = 922.
- 2018, Zeng X, Onco Targets Ther, gastric cancer, n = 2,856; 897 after prop. match.
- 2018, Oh TK, Cancer Control, non-small cell lung cancer, n = 943; propensity matching produced 196 patients in each group.

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Valet av sömnmedel, propofol vs inhalation

Pågående studier, registrerade vid ClinicalTrials.gov

Sponsor	Akronym	Randomisering	Utfall	Cancer- lokalisering	Antal	Start	Slut
Stony Brook University, New York	GA- CARES	TIVA vs Inhal.	Död, alla orsaker, 2 år	Blandat	2 000	2017	2020
Peking University First Hospital, Beijing		Propofol vs sevofluran	Överlevnad, 1, 2 och 3 år	Blandat	1 200	2015	2020
CKF-Västerås/ Uppsala Universitet	CAN	Propofol vs sevofluran	Överlevnad, 1 och 5 år	Bröst och kolo- rektal	8 000	2013	2023

CAN-studien

Powerberäkning

Sample size calculation

Expected 5-year survival

breast cancer 85% (82% vs. 87%)

80% power, 5% significance, total: 1,650 pts

colon cancer 60% (55% vs. 60%)

80% power, 5% significance, total: 3,000 pts

rectal cancer 70% (65% vs. 70%)

80% power, 5% significance, total: 2,490 pts

Marginal 860 pts

Total 8,000 pts

CAN status 2018-05-02

Participating sites

Currently, the study is ongoing in:

Sweden (Skellefteå, Sundsvall, Uppsala, Västerås, Örebro, Kalmar, Helsingborg, Lund)

Poland (Wrocław)

Kina (Beijing)

The study is coordinated and financed from Västerås*.



CAN study

ABOUT THE STUDY NEWS PARTICIPANTS FUNDINGS MONITORING MEETINGS CONTACTS



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Blockadteknikers roll

The Ochsner Journal

[Ochsner J.](#) 2017 Winter; 17(4): 345–361.

PMCID: PMC5718448

PMID: [29230120](#)

The Relationship Between Regional Anesthesia and Cancer: A Metaanalysis

[Ravi K. Grandhi, MD, MBA,¹](#) [Samuel Lee, MD,²](#) and [Alaa Abd-Elsayed, MD, MPH^{✉3}](#)

[Author information ▶](#) [Copyright and License information ▶](#) [Disclaimer](#)

Conclusion:

This metaanalysis shows that RA has no overall survival, recurrence-free survival, or biochemical recurrence-free survival benefit. However, some individual studies have shown significant benefit in terms of cancer recurrence. Further, RA reduces the use of opioids, which has led to some secondary benefits. Further studies are needed to establish the benefits of RA as it relates to cancer.

Sammanlagt 28 studier, varav
24 retrospektiva, 1 prospektiv icke-randomiserad och 3 RCT

Blockadteknikers roll

Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in Central Sweden.

Gupta A, et al. Br J Anesth 2011;107:164-70.

n = 93 + 562



CONCLUSION

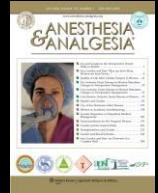
We found a reduction in all-cause mortality after rectal but not colon cancer in patients having EDA compared with PCA technique.

Blockadteknikers roll

Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia.

Christopherson R, et al. Anesth Analg 2008;107:325-32.

n = 92 + 85



CONCLUSION

Epidural supplementation was associated with enhanced survival among patients without metastases before 1.46 years. Epidural anesthesia had no effect on survival of patients with metastases.

Blockadteknikers roll

Epidural anesthesia and cancer recurrence rates after radical prostatectomy.

Tsui BC, et al. Can J Anaesth 2010;57:107-12.

n = 50 + 49



CONCLUSION

No difference was observed between the epidural and control groups in disease-free survival at a median follow-up time of 4.5 years.

Blockadteknikers roll

Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence free survival: a randomised trial.

Myles PS, et al. BMJ 2011;342:d1491.

n = 216 + 230



BMJ
Open

CONCLUSION

Use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival.

Blockadteknikers roll

Nu ser vi fram emot resultatet från EPICOL, en svensk multicenter-studie som drivs från Örebro-Linköping.

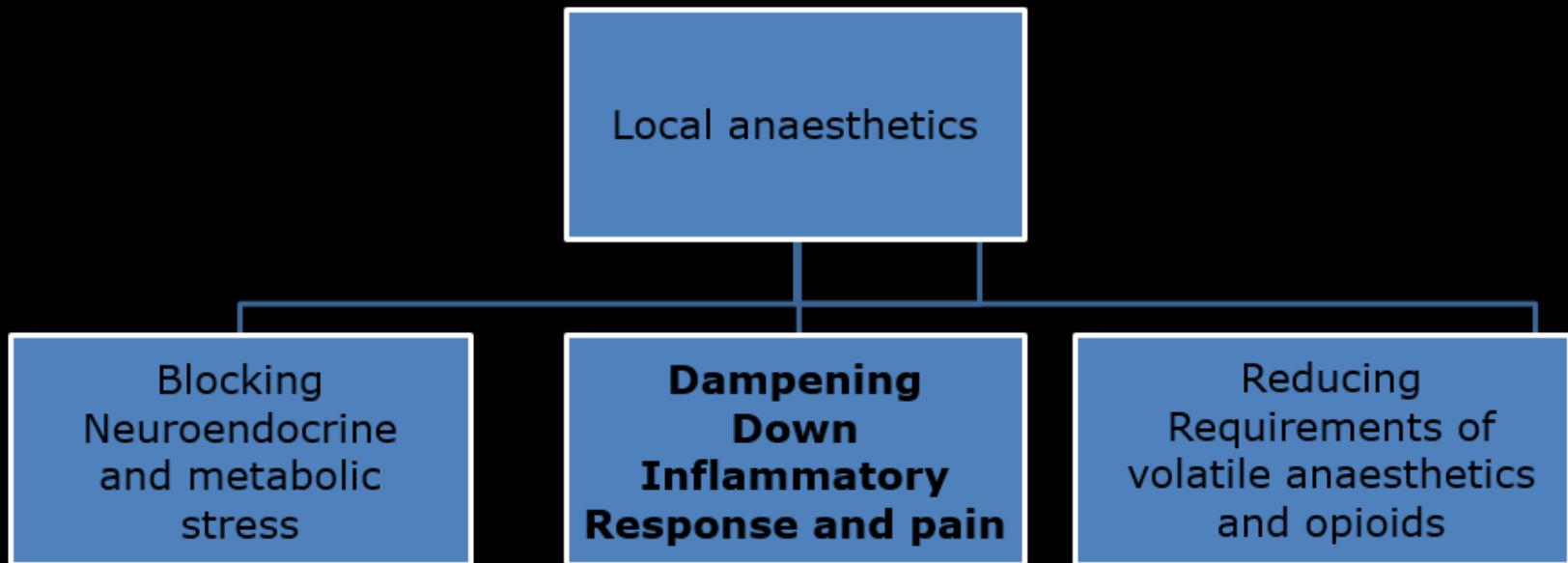
n = 140 + 140



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Effekter av lokalanestestika utöver själva blockaden



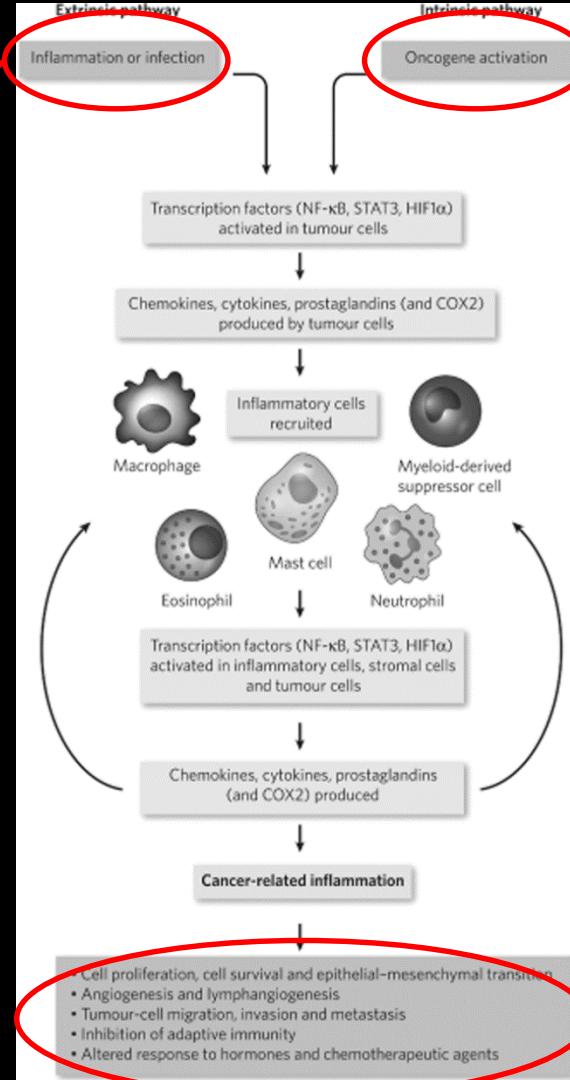
Tavare AN, et al. Int J Cancer 2012;130:1237-50



Effekter av lokalanestestika utöver själva blockaden

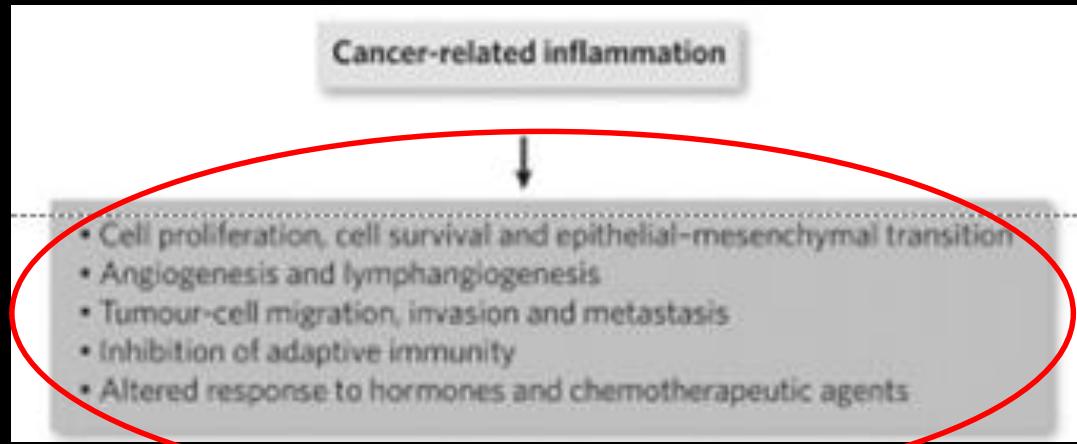
Inflammation
och infektion

Onkogen
aktivering



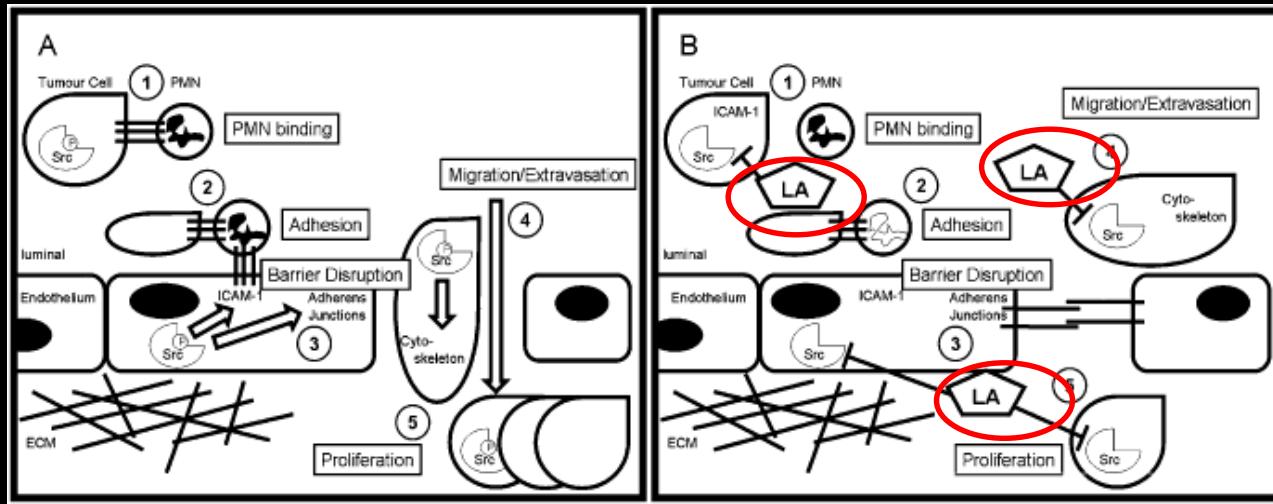
Votta-Velis EG, et al.
Acta Anaesthesiol Scand
2013;57:12111-29

Effekter av lokalanestestika utöver själva blockaden



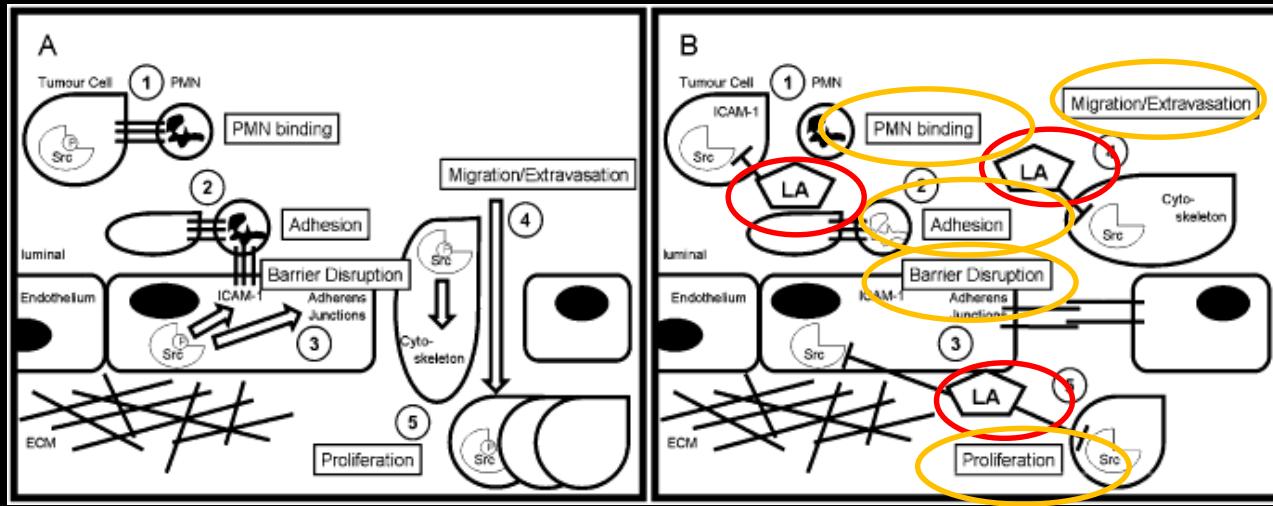
Votta-Velis EG, et al.
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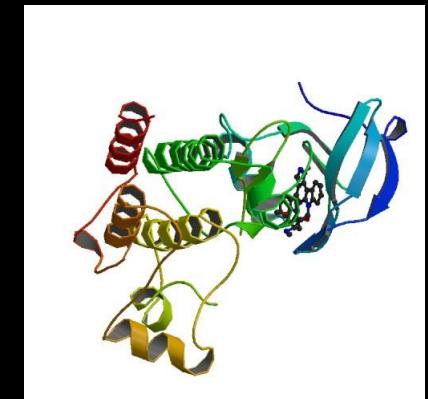
Votta-Velis EG, et al.
Acta Anaesthesiol Scand
2013;57:12111-29

Src and cancer

Src protein kinase

- Src is involved in signaling epithelial-to-mesenchymal transformation
- It also promotes cell survival and mitogenesis and has a profound effect on the cytoskeleton during cell migration
 - all of that is necessary for solid tumor metastasis!
- Commercially available: FDA-approved Src-inhibitors (e.g. for GIST)

Inflammatory signaling plays a crucial role in the development, growth and metastasis of cancer



Guarino M, J Cell Physiol 2010;223:14-26
Thiery JP, Nat Rev Cancer 2002;2(6):442-454

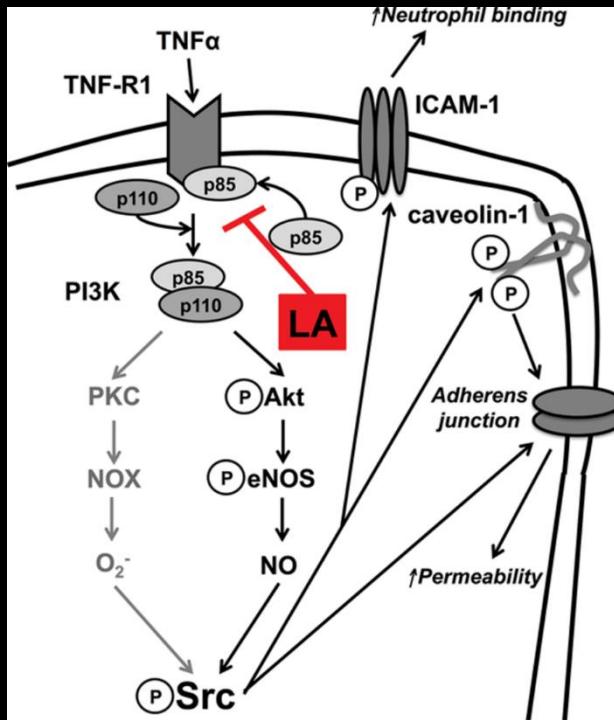
Effekter av lokalanestestika utöver själva blockaden



From: Endothelial Barrier Protection by Local Anesthetics: Ropivacaine and Lidocaine Block Tumor Necrosis Factor- α -induced Endothelial Cell Src Activation

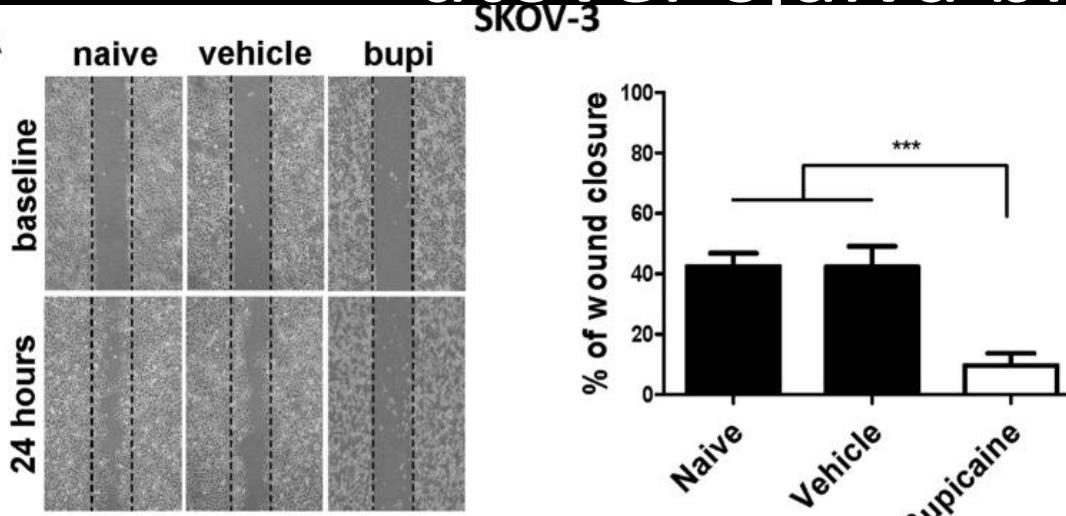
Anesthes. 2014;120(6):1414-1428. doi:10.1097/ALN.0000000000000174

Piegeler T, Votta-Velis EG, Bakhshi FR, Mao M, Carnegie G, Bonini MG, Schwartz DE, Borgeat A, Beck-Schimmer B, Minshall RD.

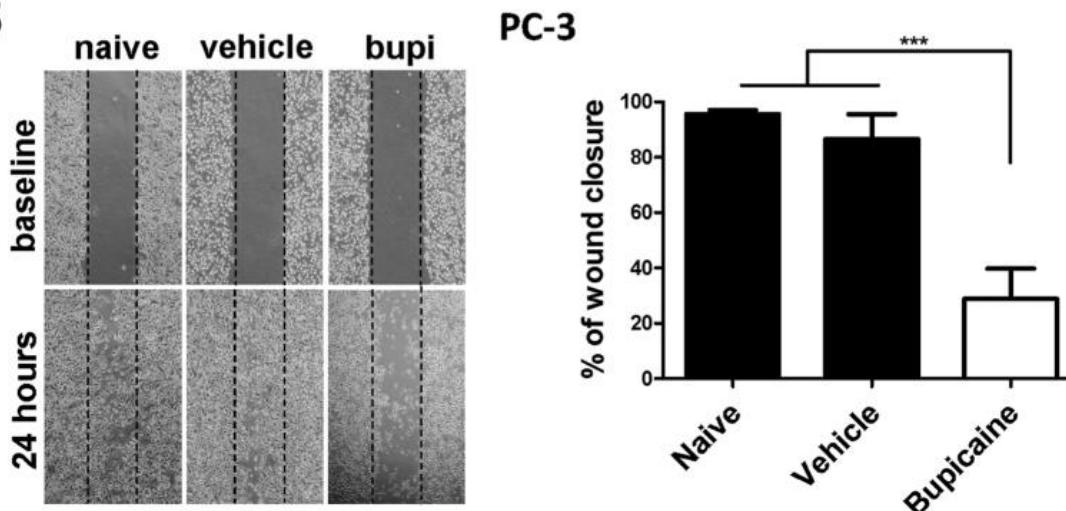


Effekter av lokalaneestestika utöver själva blockaden

A



B



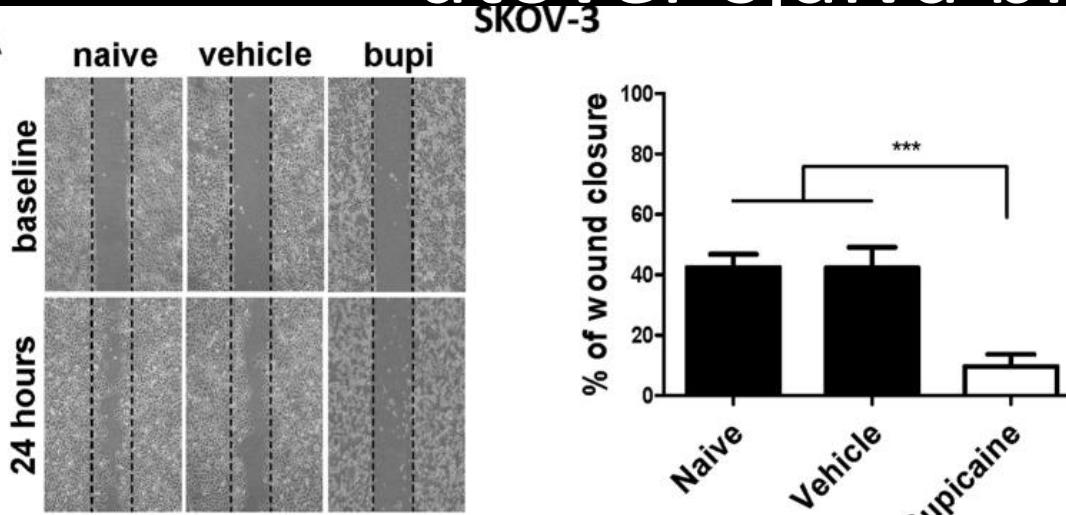
Bupivacaine treatment inhibited cell migration of both ovarian cancer (SKOV-3) and prostate cancer (PC-3) cells

Wei X, et al. Sci Rep 2016;6:26277

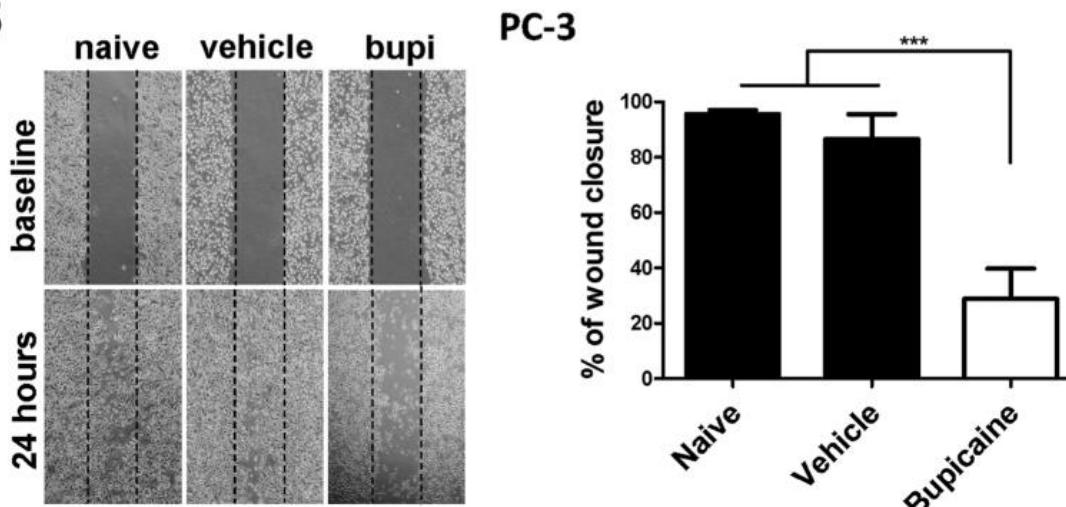


Effekter av lokalanestestika utöver själva blockaden

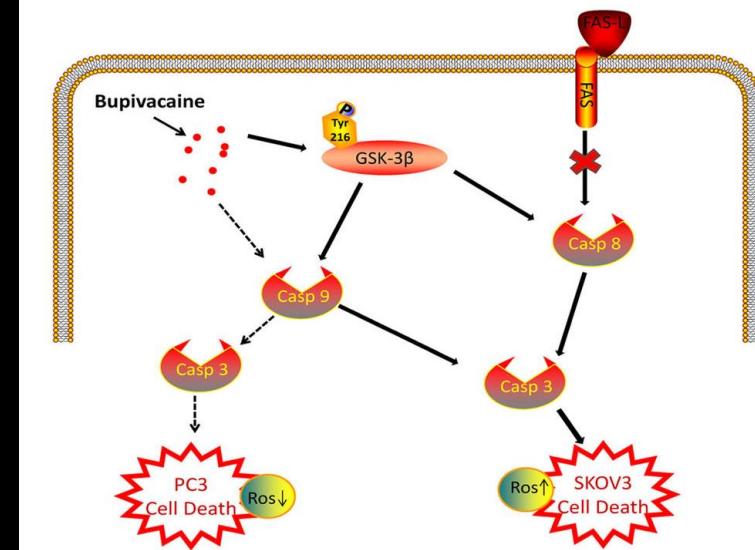
A



B



The proposed molecular mechanisms for bupivacaine induced cancer cell death



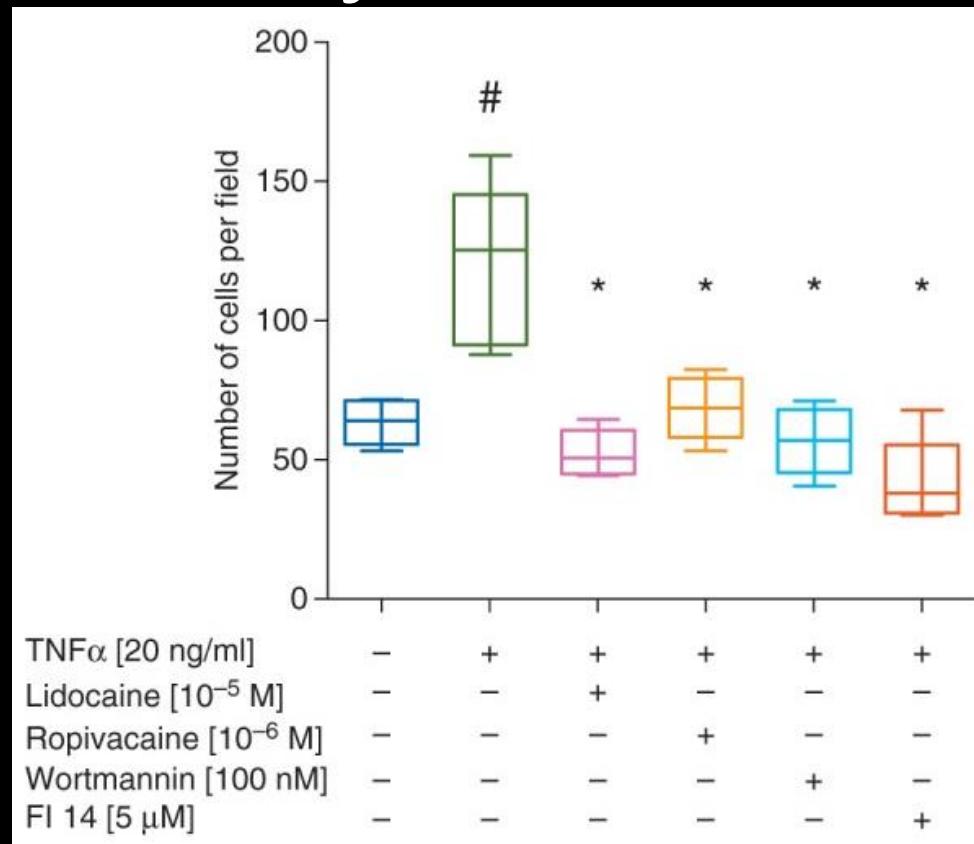
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Wei X, et al. Sci Rep 2016;6:26277





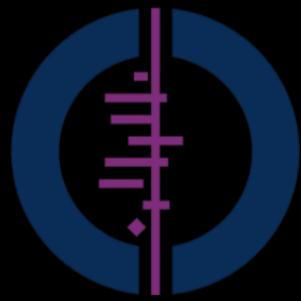
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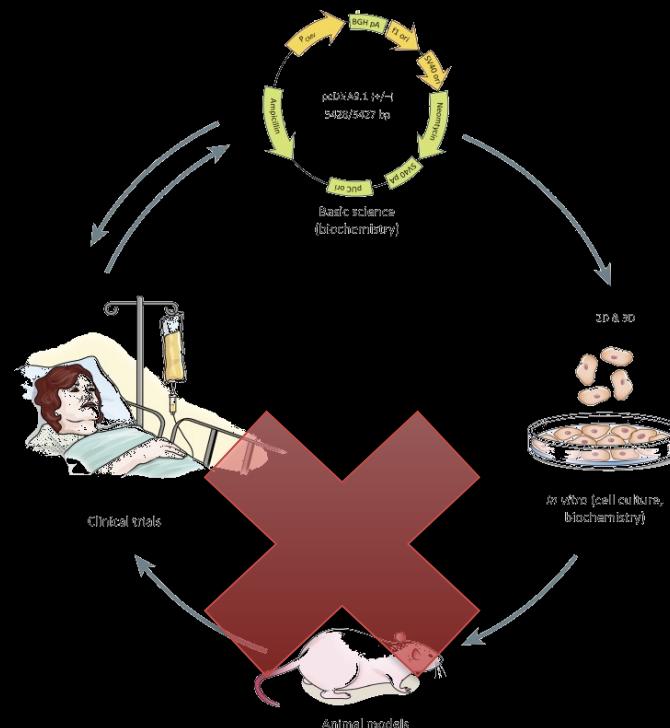
Piegeler T, et al. Br J Anaesth 2015;115:784-91

Prospective RCT?

“Compelling *in vitro* evidence, however *in vivo* data is lacking”



Cochrane





Can Perioperative Lidocaine Reduce Metastasis in a Mouse Model of Breast Cancer?

Delaney Medal Presentation
5-5-17

*Dr Mark Johnson
Research Fellow in Anaesthesia
Mater Misericordiae University
Hospital & University College Dublin*



Hypothesis

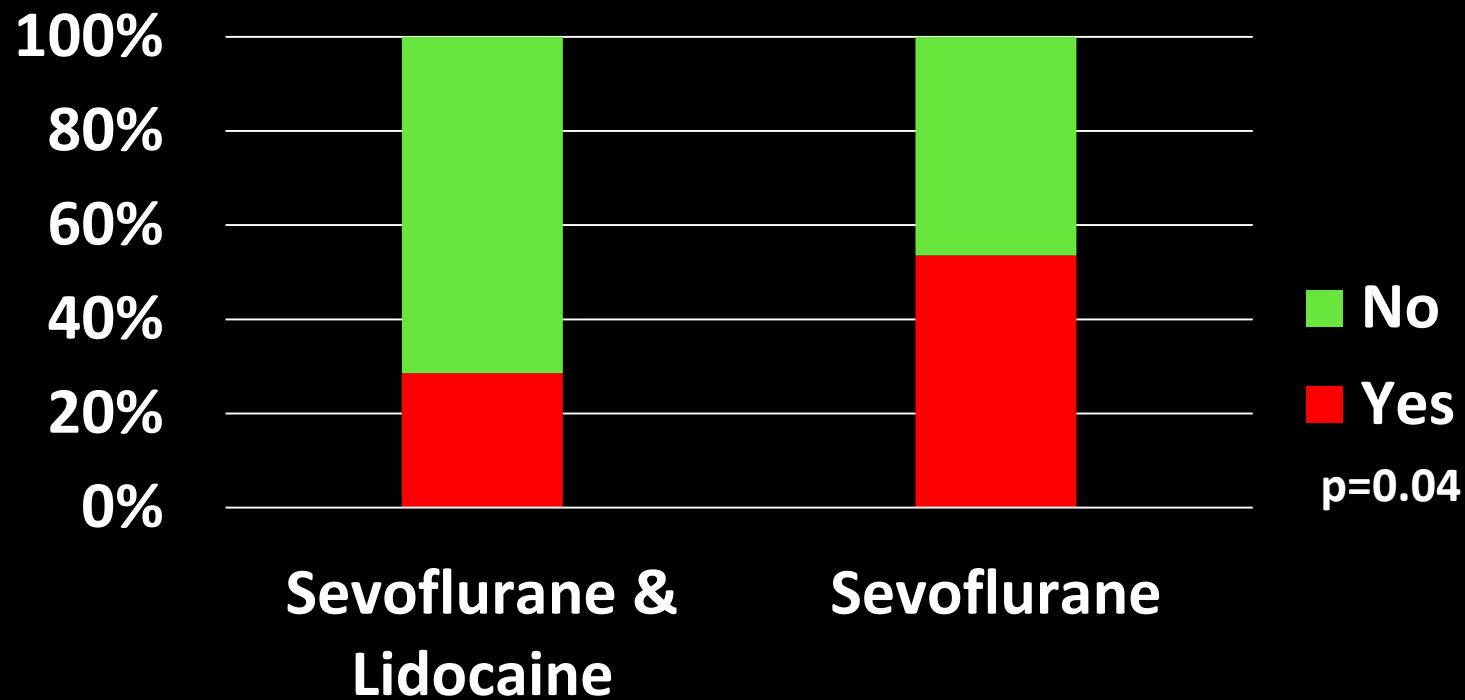
Perioperative amide local anaesthetic infusion during primary tumour resection attenuates pulmonary metastatic disease in a mouse model of breast cancer

A. Inhalational model: Sevoflurane

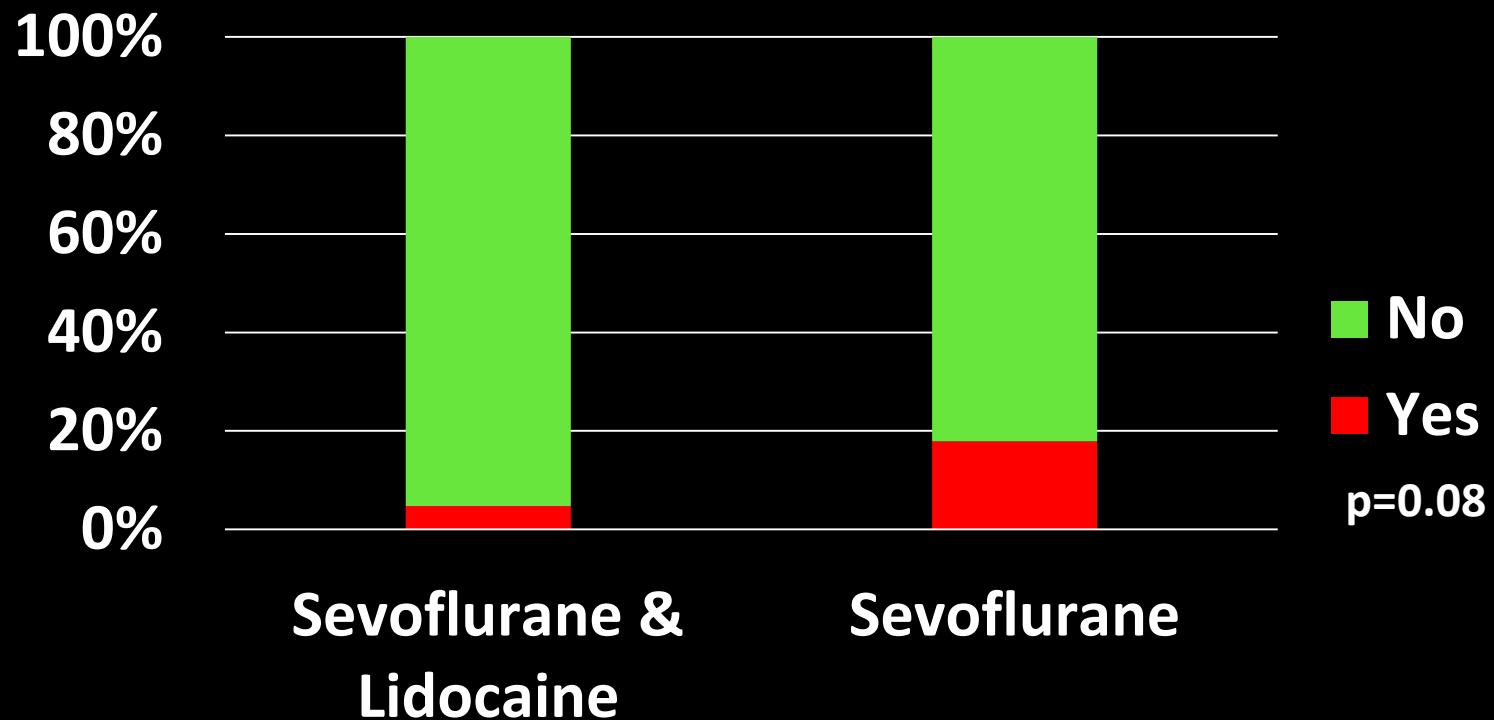
B. Injectable model: Ketamine & Xylazine

Sevoflurane ± Lidocaine

Detectable Pulmonary Metastasis



Sevoflurane \pm Lidocaine Local Recurrence



Conclusions

- IV Lidocaine reduces pulmonary metastasis when combined with Sevoflurane anaesthesia
- No protective effect when combined with Ketamine/ Xylazine anaesthesia

Effekter av lokalanestestika utöver själva blockaden

- Klinisk studie kommer att starta med infusion av lidocaine eller placebo till pat. med pancreascancer.
- Alain Borgeat och Gina Votta-Velis har fått ett anslag på 200 000 USD.



Kan anestesiteknik påverka utfall efter cancerkirurgi?

1. Valet av sömnmedel: resultat kommer
2. Blockadteknikers roll: resultat kommer
3. Effekter av lokalanevestetika: resultat kommer

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