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UNIVERSITY OF COPENHAGEN

REGION SJÆLLAND
SJÆLLANDS UNIVERSITETSHOSPITAL
– vi er til for dig

NSAID til postoperativ smertebehandling

DASAIMs Obstetrisk Symposium 2024

Prof. Ole Mathiesen

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Smerte efter kejsersnit

- Karakteristika
  - Abdominal væg + visceral smerte uterus
  - 80% har moderat to svær smerte 1 døgn
- Persisterende/kronisk smerte 10-15%
- Insufficient smertebehandling associeret med
  - Dårlig amning og omsorg for baby
  - Postpartum depression
  - Lav patient tilfredshed

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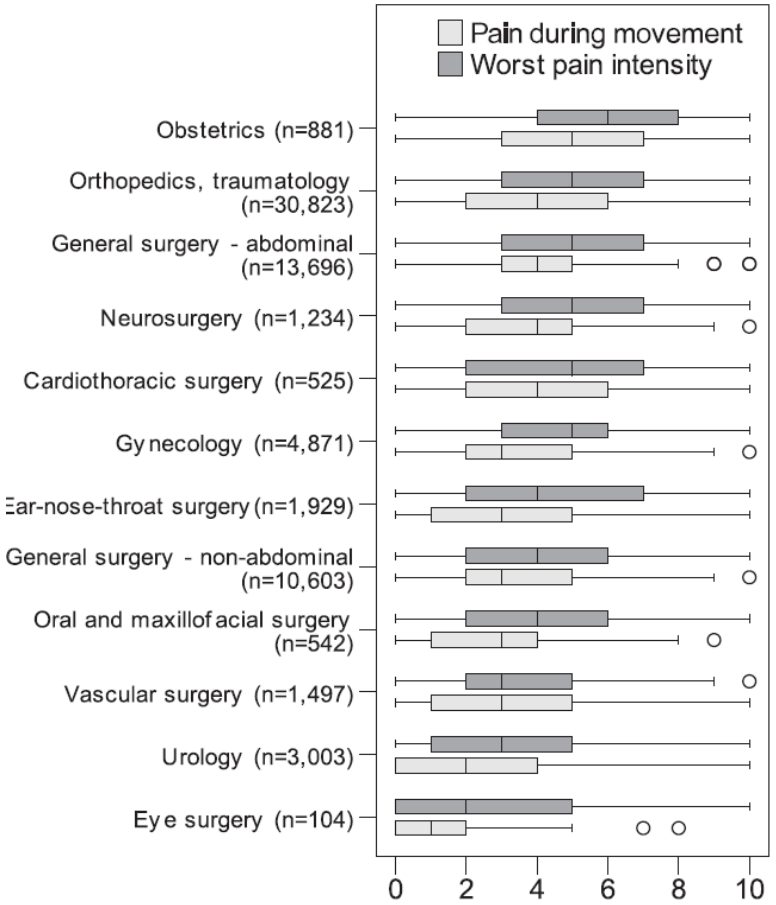
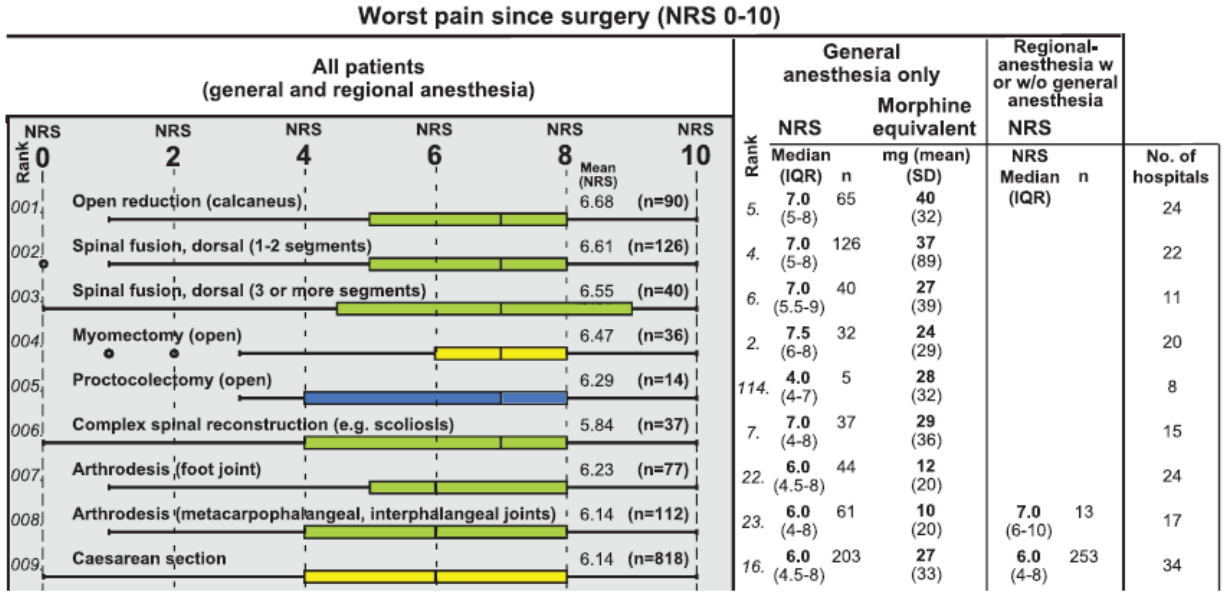
Pain Intensity on the First Day after Surgery

A Prospective Cohort Study Comparing 179 Surgical Procedures

Hans J. Gerbershagen, M.D., Ph.D.,* Sanjay Aduckathil, M.D.,† Albert J. M. van Wijck, M.D., Ph.D.,‡ Linda M. Peelen, Ph.D.,§ Cor J. Kalkman, M.D., Ph.D.,‖ Winfried Meissner, M.D., Ph.D.#





Rank	General anesthesia only: NRS Median (IQR)	n	Morphine equivalent mg (mean) (SD)	Regional-anesthesia w or w/o general anesthesia: NRS Median (IQR)	n	No. of hospitals
5.	**7.0** (5-8)	65	**40** (32)			24
4.	**7.0** (5-8)	126	**37** (89)			22
6.	**7.0** (5.5-9)	40	**27** (39)			11
2.	**7.5** (6-8)	32	**24** (29)			20
114.	**4.0** (4-7)	5	**28** (32)			8
7.	**7.0** (4-8)	37	**29** (36)			15
22.	**6.0** (4.5-8)	44	**12** (20)			24
23.	**6.0** (4-8)	61	**10** (20)	**7.0** (6-10)	13	17
16.	**6.0** (4.5-8)	203	**27** (33)	**6.0** (4-8)	253	34

Anesthesiology 2013; 118:934-44

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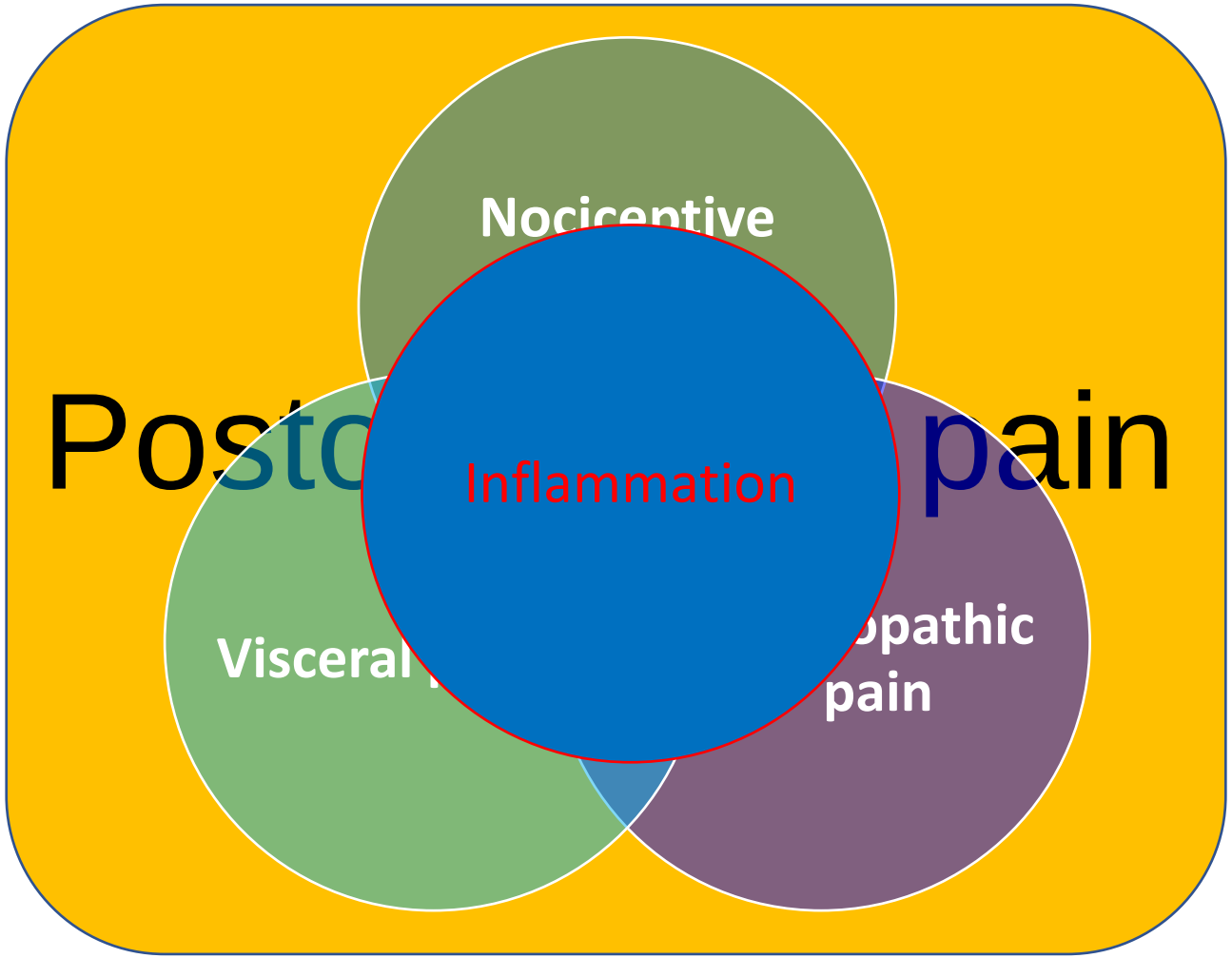

Visceral pain

- Diffuse & difficult to locate
  - Receives signals from larger areas of viscera and deep tissue
  - 90% nociceptive – 10% visceral
- Convergence:
  - Each dorsal horn neuron receive input from several neurons
  - Hereby receives pain from skin and muscle that belong to same segment
  - Referred pain

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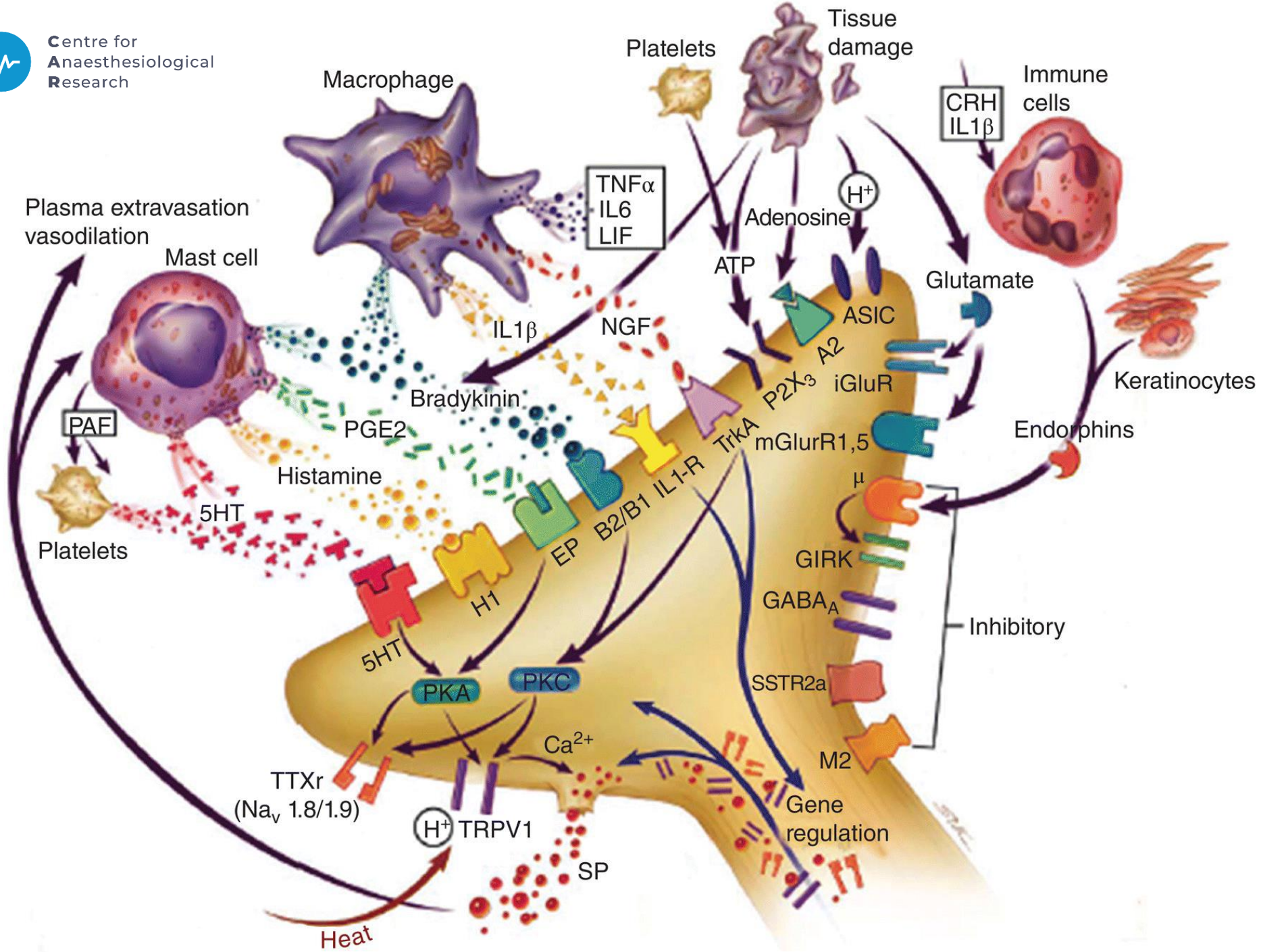
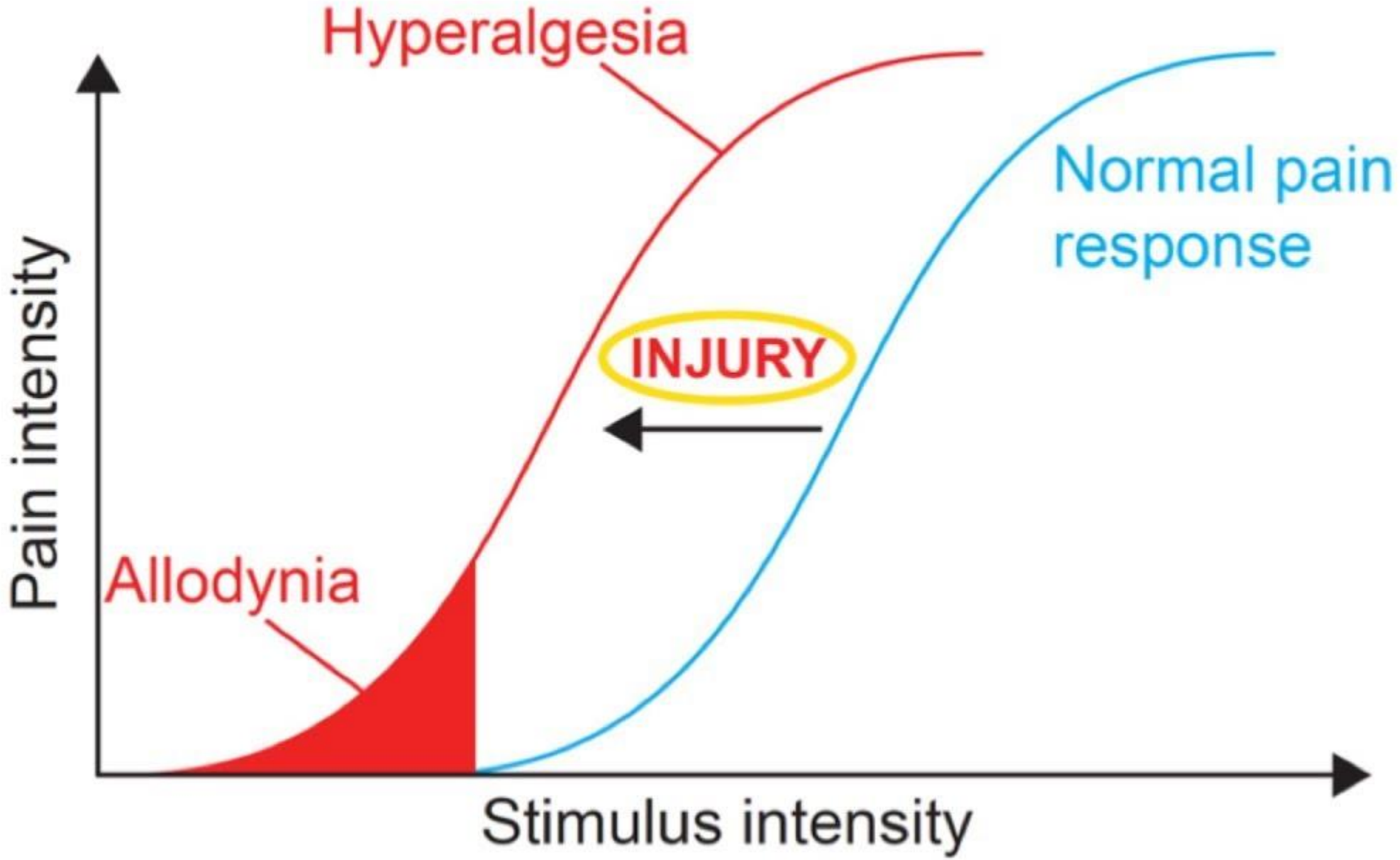


Inflammatory ‘soup’

- Neurotransmitters
- Peptides
- Eicosanoids
- Neruotrhopins
- Nucleotides
- Nerve growth factor
- Proteases and protons
- Cytokines (IL-1 /-6 and TNF-alfa)
- ATP
- Bradykinin
- Histamin
- Serotonin
- Prostaglandin (PGE)

Peripheral and central sensitization


Hyperalgesia
Normal pain
response
INJURY
Pain intensity
Allodynia
Stimulus intensity

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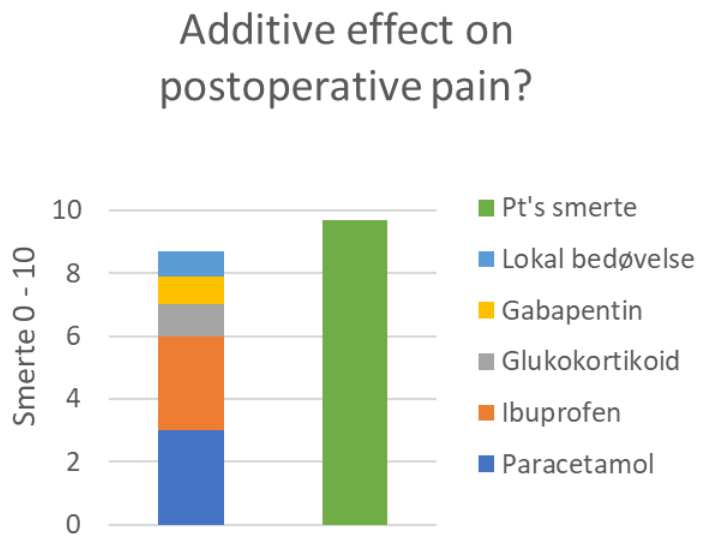
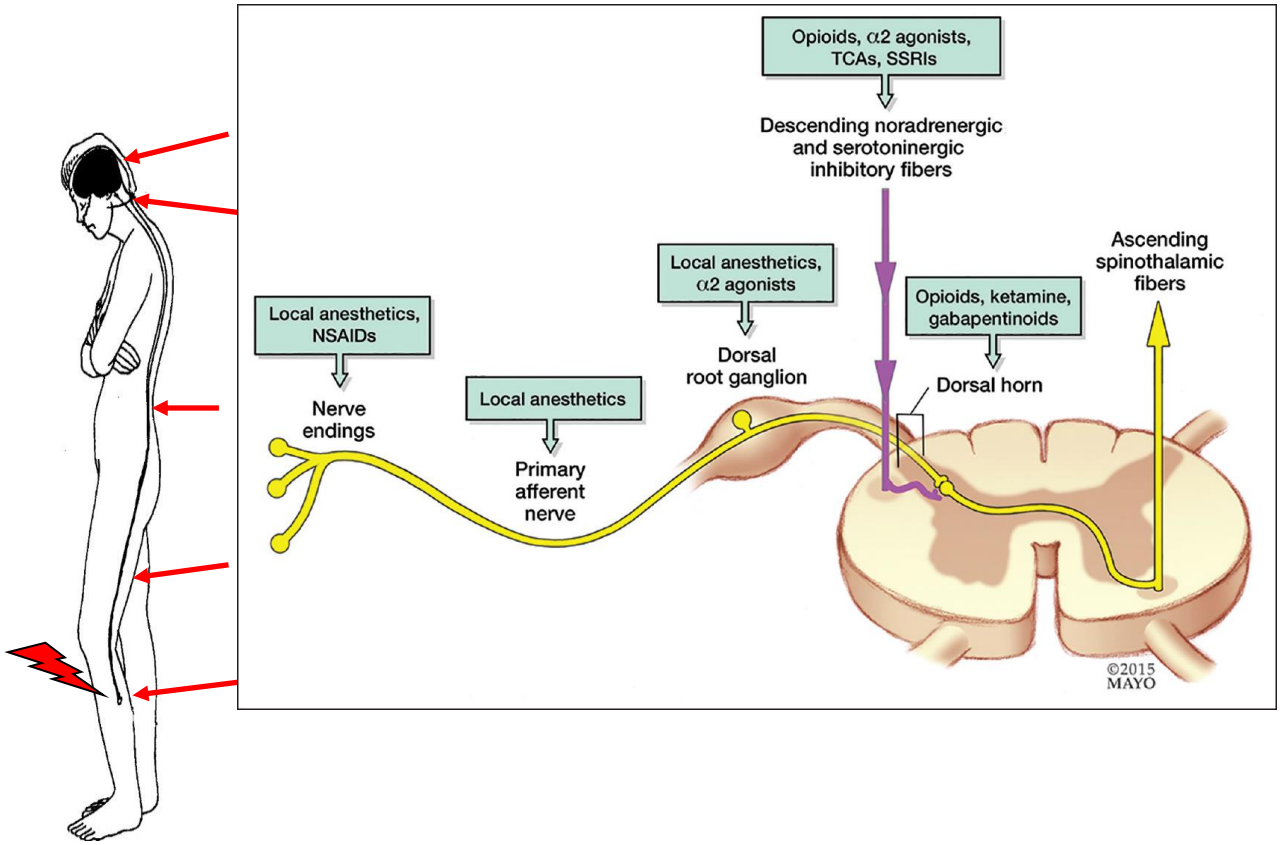
Multimodal/balanced pain treatment

- Combination of analgetics
- Additive effect
- Better pain treatment
- Less adverse effects / opioid-related adverse effects





Analgetisk effekt af non-opioide analgetika

Drug	24h opioid reduction	Pain	Opioid related AE
PCM	6-9 mg	+	+
NSAID	>10 mg	+	+
Glucocorticoids	2-5 mg	+	+
Gabapentin	3-8 mg	+	+
Pregabalin	5-8 mg	+	+
Gabapentinoids	8 mg	+	+
Ketamine	8 mg	+	+
Clonidine	(24%, 4 RCT)	-	+

References	Reviews
PCM	Remy, 2005; Elia 2005; Toms 2008; Tzortzopoulou 2011; McDaid 2010; Apfel, 2013, McNicol 2016, Mallama 2021
NSAID	Maund 2011, Elia 2005, Marret 2005, Bainbridge 2006, De Oliveira 2012
GCC	De Oliveira 2011, Waldron 2013, Køppen 2022 (submitted)
GABA	Fabritius 2016, Doleman 2015
PREGABA	Fabritius 2017, Eipe 2015, Mishriky 2015
Gabapentionoids	Verret 2020
Ketamine	Brinck 2018,
Clonidine	Munoz 2017

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Basic postopertaive analgesic recipé for most of patients

Priority	Analgesic	Dose	OBS	PREOP	PERIOP	POSTOP
1	PCM	1g x 4		X	(IV)	X
2	Ibuprofen	400 mg x 3-4	Cardiac Ulcus Kidney	X (Celecoxib if bleeding)		X (< 7 days)
3 (if 1+2 is insuf-ficient)	Dexamethasone / Methyl-prednisolone	16-24 mg / 125 mg	Single dose! (Repeat dose: TKA)	(X)	X	(X)
4 (if 1+2+3 is insuf-ficient)	Gabapentin	300-600 mg	Elderly Opioid (Sedation)	X		X (300 + 600 mg)
Where relevant	Epidural infusion			X	X	X
Where relevant	Regional anaesthesia/block		Duration / rebound pain	X	X	X
Allways –if needed	Opioids	0.1 mg/kg	½ dose elderly			X

Anaesthesia 2022, 76, 665-680 doi:10.1111/anae.15339

Guidelines

PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations

E. Roofthooft,[1,2] G. P. Joshi,[3] N. Rawal,[4] M. Van de Velde,[5] and on behalf of the PROSPECT

- IT morphine 50-100 ug SA / epidural morphine 2-3 mg
- OR or IV PCM
- IV and OR NSAID
- Analgetic and anti-emetic: Dexamethasone IV (dose?)
- LIA / Fascial plane block

May 2021 • Volume 132 • Number 5 www.anesthesia-analgesia.org

Society for Obstetric Anesthesia and Perinatology: Consensus Statement and Recommendations for Enhanced Recovery After Cesarean

Laurent Bollag, MD,* Grace Lim, MD, MS,† Pervez Sultan, MBChB, FRCA, MD (Res),‡ Ashraf S. Habib, MBBCh, MSc, MHSc, FRCA,§ Ruth Landau, MD,‖ Mark Zakowski, MD,¶ Mohamed Tiouririne, MD,# Sumita Bhambhani, MD,** and Brendan Carvalho, MBBCh, FRCA, MDCH‡

- IT morphine 50-150 ug SA / epidural morphine 1-3 mg
- IV and OR PCM
- IV and OR NSAID
- Anti-emetic: Ondansetron 4 mg / dexamethasone 4 mg
- LIA / TAP / QLB

ANESTHESIOLOGY

Postoperative Analgesic Effectiveness of Quadratus Lumborum Block for Cesarean Delivery under Spinal Anesthesia

A Systematic Review and Meta-analysis

Nasir Hussain, M.D., M.Sc., Richard Brull, M.D., F.R.C.P.C., Tristan Weaver, M.D., Meiqin Zhou, M.D., Michael Essandoh, M.D., Faraj W. Abdallah, M.D., M.Sc.

ANESTHESIOLOGY 2021; 134:72–87

Same for pain

Et studie på Anterior QL med NS

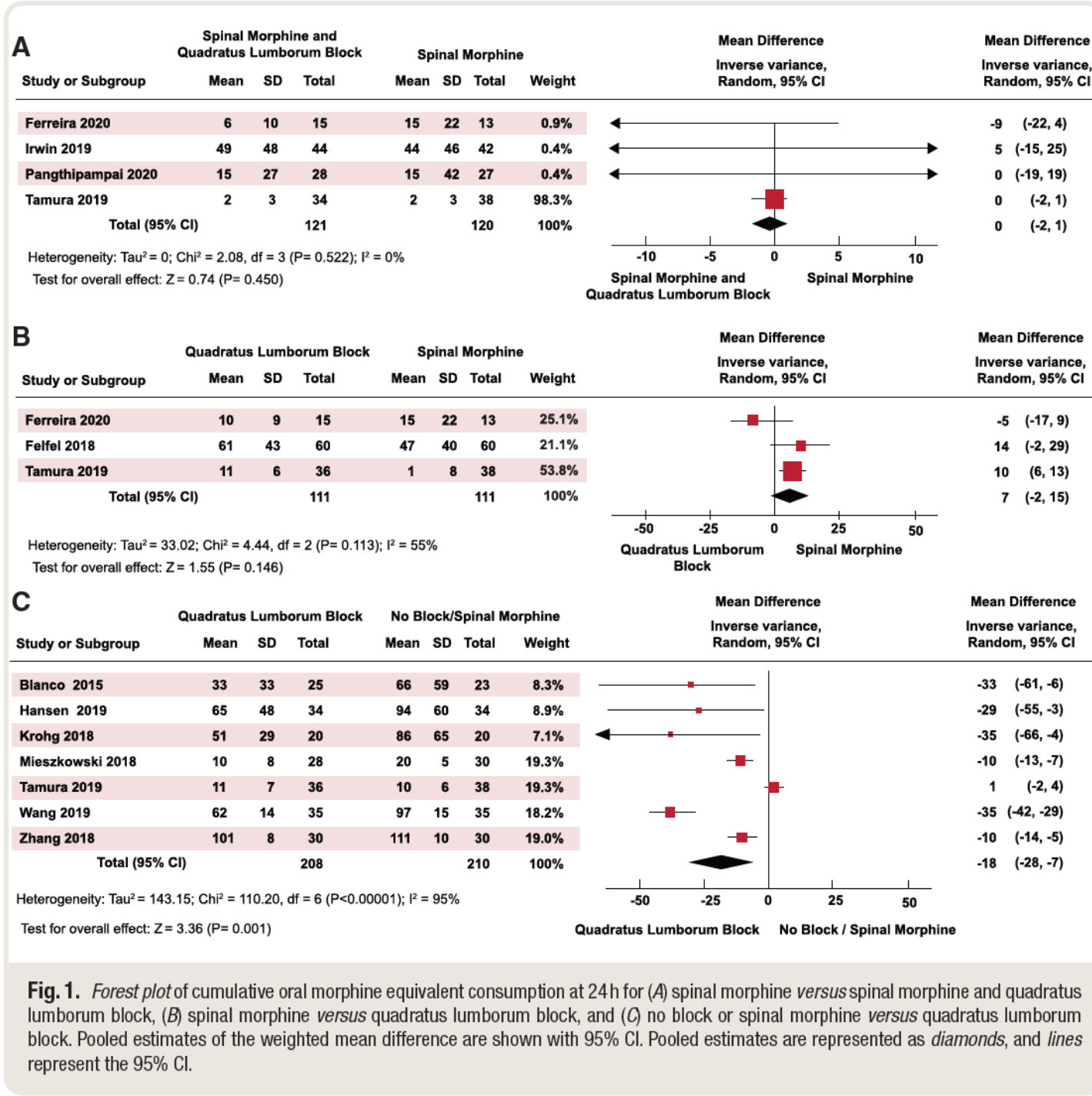
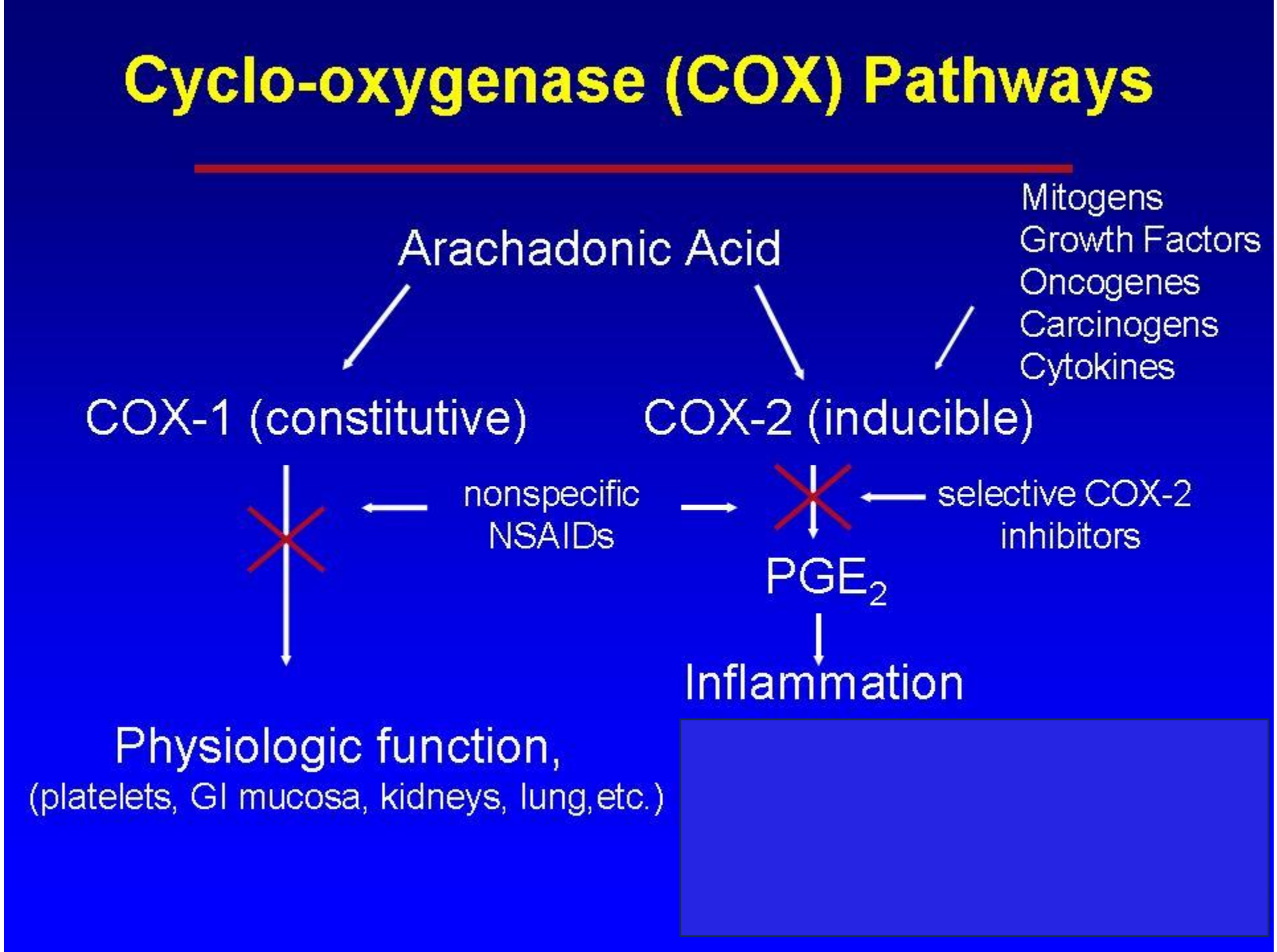


Fig. 1. *Forest plot* of cumulative oral morphine equivalent consumption at 24 h for (*A*) spinal morphine *versus* spinal morphine and quadratus lumborum block, (*B*) spinal morphine *versus* quadratus lumborum block, and (*C*) no block or spinal morphine *versus* quadratus lumborum block. Pooled estimates of the weighted mean difference are shown with 95% CI. Pooled estimates are represented as *diamonds*, and *lines* represent the 95% CI.

Cyclo-oxygenase (COX) Pathways



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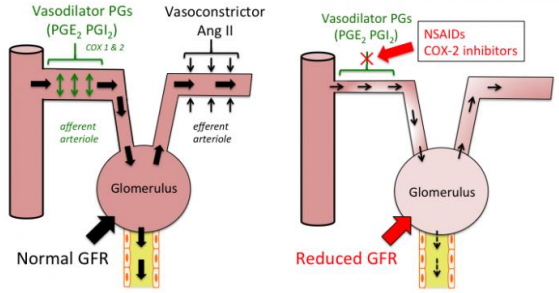
NSAIDs and risk of harm

- Renal function
  - Reversible effect in most patients
  - Take care in high risk patients:
    - Elderly
    - Peroperative low blood pressure (ATIN)
    - Low kidney function



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Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction - A Nationwide Cohort Study

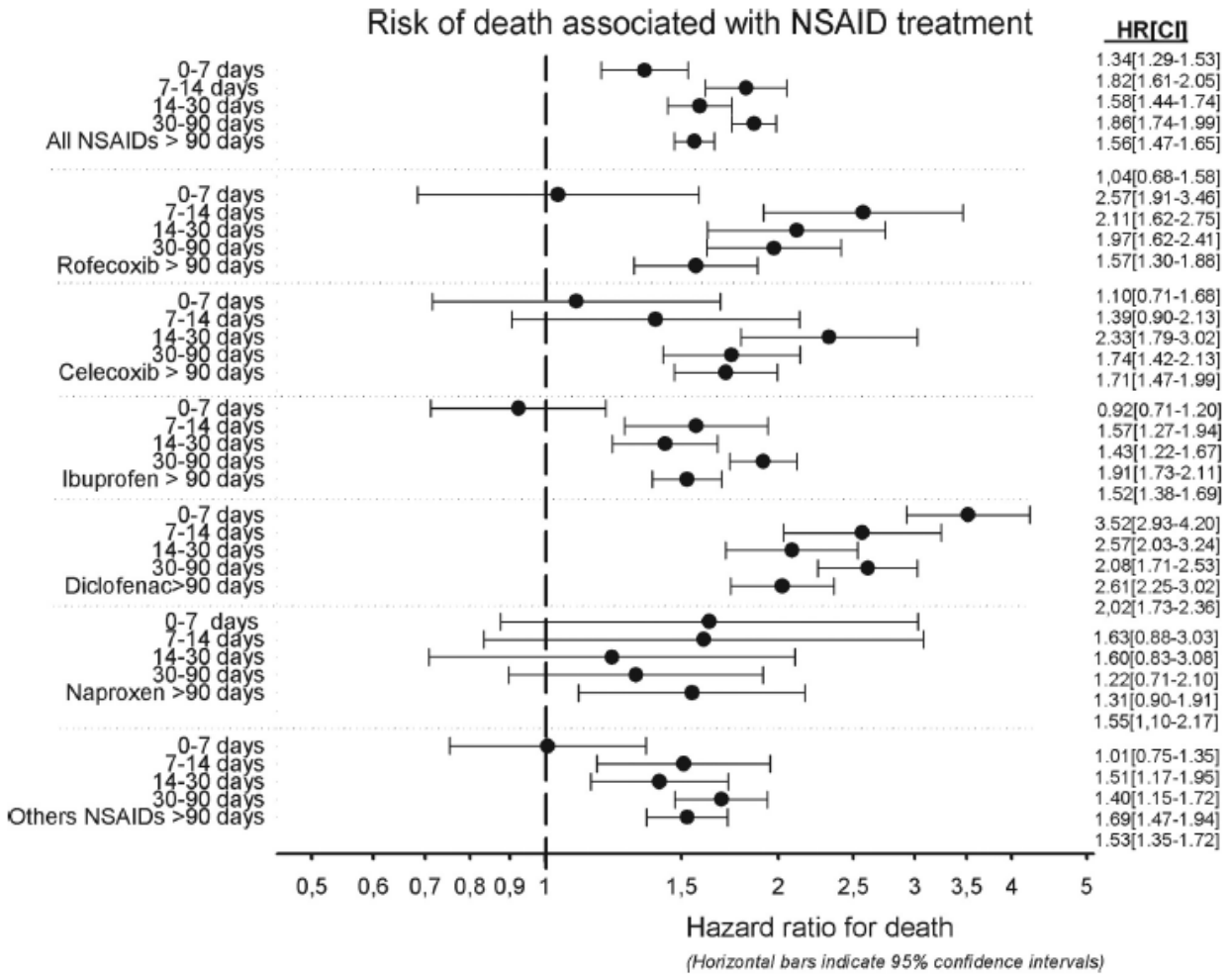

Figure 3. Time-dependent Cox proportional hazard analysis of risk of death according to duration of nonsteroidal antiinflammatory drug (NSAID) treatment in patients with prior myocardial infarction. HR indicates hazard ratio; CI, confidence interval.

Registry study
Included co-horte:

- 83677 pt's > 30 yr
- 1997-2006
- First time AMI
- Analyses linked to NSAID prescriptions from pharmacies in DK

Schjerning Olsen AM
Circulation 2011

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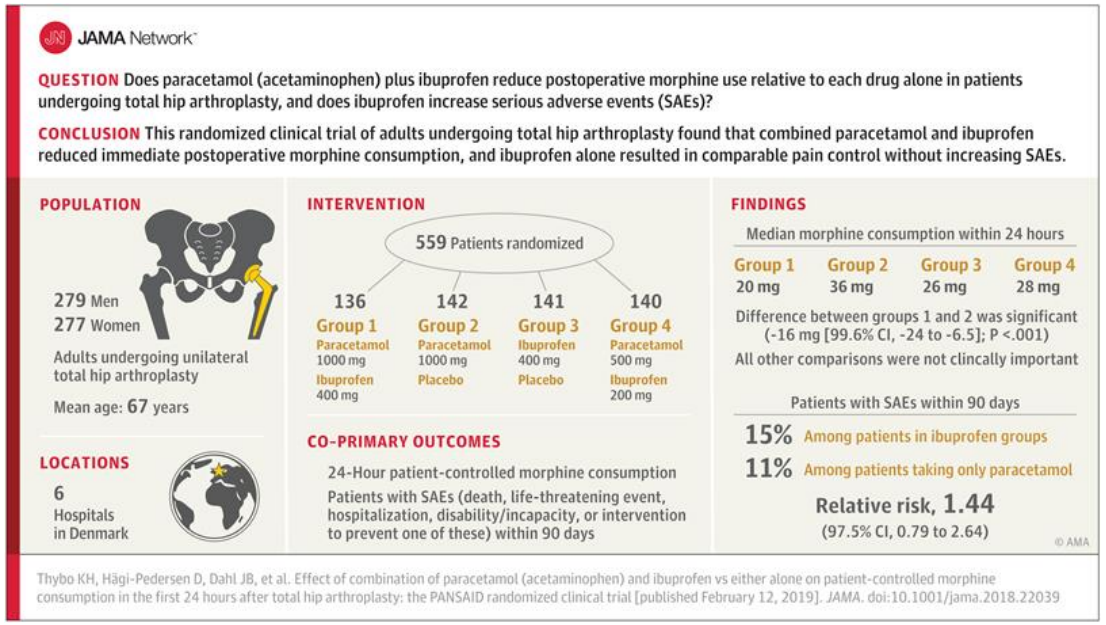
JAMA | Original Investigation

Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty

The PANSAID Randomized Clinical Trial

Kasper Højgaard Thybo, MD; Daniel Hägi-Pedersen, PhD; Jørgen Berg Dahl, DMsci; Jørn Wetterslev, PhD; Mariam Nersesjan, MS; Janus Christian Jakobsen, PhD; Niels Anker Pedersen, MD; Søren Overgaard, DMsci; Henrik M. Schrøder, MD; Harald Schmidt, MD; Jan Gottfrid Bjørck, MD; Kamilla Skovmand, PhD; Rune Frederiksen, MD; Morten Buus-Nielsen, MD; Charlotte Voss Sørensen, BSN; Laura Smedegaard Kruuse, MS; Peter Lindholm, MD; Ole Mathiesen, PhD



Thybo KH, Hägi-Pedersen D, Dahl JB, et al. Effect of combination of paracetamol (acetaminophen) and ibuprofen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty: the PANSAID randomized clinical trial [published February 12, 2019]. *JAMA*. doi:10.1001/jama.2018.22039

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Dizziness, 24 hours %	**19**	**23**	**29**	**27**
Group PCM+IBU*	-	0.83 (0.52 to 1.32) P=.43	0.67 (0.44 to 1.04) P=.077	0.71 (0.46 to 1.10) P=.13
Group PCM*	-	-	0.81 (0.54 to 1.22) P=.31	0.85 (0.57 to 1.28) P=.44
Group IBU*	-	-	-	1.05 (0.72 to 1.54) P=.80
Vomiting, 0-24 hours, number, median	**0**	**0**	**0**	**0**
Group PCM+IBU**	-	0 (0 to 0) P=.47	0 (-1 to 0) P=.96	0 (0 to 1) P=.20
Group PCM**	-	-	0 (-1 to 0) P=.36	0 (0 to 1) P=.55
Group IBU**	-	-		0 (0 to 1) P=.13
Ondansetron, mg**	**0**	**0**	**0**	**0**
Group PCM+IBU**	-	0 (-2 to 0) P=.09	0 (0 to 0) P=.86	0 (-2 to 0) P=.038
Group PCM**	-	-	0 (0 to 2) P=.15	0 (-2 to 2) P=.73
Group IBU**	-	-	-	0 (-2 to 0) P=.050
Blood loss, ml	**300**	**300**	**265**	**287.5**
Group PCM+IBU**	-	0 (-60 to 52.5) P=.90	35 (-25 to 85) P=.29	12.5 (-50 to 65) P=.36
Group PCM**	-	-	35 (-20 to 100) P=.19	12.5 (-50 to 50) P=.37
Group IBU**	-	-	-	-22.5 (-75 to 50) P=.85
Days alive and outside hospital, days	**89**	**88**	**88**	**88**
Group PCM+IBU**	-	1 (-1 to 1) P=.46	1 (-1 to 1) P=.13	1 (-2 to 1) P=.55
Group PCM**	-	-	0 (-1 to 2) P=.69	0 (-1 to 1) P=.94
Group IBU**	-	-	-	0 (-2 to 1) P=.56

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Non-opioid analgesic combinations following total hip arthroplasty (RECIPE): a randomised, placebo-controlled, blinded, multicentre trial

Lancet Rheumatol 2024

*Joakim Steiness, Daniel Hägi-Pedersen, Troels Haxholdt Lunn, Søren Overgaard, Stig Brorson, Ben Kristian Graungaard, Martin Lindberg-Larsen, Claus Varnum, Lars Hyldborg Lundstrøm, Torben Beck, Michael Skettrup, Niels Anker Pedersen, Manuel Josef Bieder, Adam Gregers von Cappeln, Lina Pleckaitiene, Peter Lindholm, Syed Shaheer Haider Bukhari, Cecilie Bauer Derby, Maria Gantzel Nielsen, Oskar Wilborg Exsteen, Louise Ørts Vinstrup, Kasper Højgaard Thybo, Kasper Smidt Gasbjerg, Anders Kehlet Nørskov, Janus Christian Jakobsen, and Ole Mathiesen, for the RECIPE trial group**

Interpretation In adults undergoing total hip arthroplasty, a combination of paracetamol, ibuprofen, and dexamethasone had the lowest morphine consumption within 24 h following surgery and the most favourable adverse event profile, with a lower incidence of serious and non-serious adverse events (primarily driven by differences in nausea, vomiting, and dizziness) compared with paracetamol plus ibuprofen.

RECIPE

	Paracetamol plus ibuprofen plus dexamethasone (n=258)	Ibuprofen plus dexamethasone (n=262)	Paracetamol plus dexamethasone (n=262)	Paracetamol plus ibuprofen (n=261)
(Continued from previous page)				
Daily use	13 (5%)	11 (4%)	9 (3%)	8 (3%)
Pain at rest VAS†	20·0 (1·5–40·0)	20·0 (4·8–35·0)	17·0 (2·5–35·0)	19·0 (0·0–40·0)
Pain during mobilisation VAS‡	45·5 (21·0–70·0)	44·0 (20·0–65·5)	41·0 (20·0–64·0)	46·0 (20·0–69·0)
Surgical characteristics				
Surgery duration, min	55 (45–68)	55 (45–69)	55 (45–69)	55 (45–70)
Surgery type				
Uncemented	203 (79%)	203 (77%)	204 (78%)	209 (80%)
Hybrid	32 (13%)	35 (13%)	33 (13%)	32 (12%)
Cemented	19 (7%)	20 (8%)	23 (9%)	18 (7%)
Not registered	2 (1%)	4 (2%)	1 (<1%)	1 (<1%)
Anaesthesia method				
Spinal	191 (74%)	201 (77%)	202 (77%)	185 (71%)
General anaesthesia	56 (22%)	47 (18%)	48 (18%)	58 (22%)
Conversion from spinal to general anaesthesia	11 (4%)	14 (5%)	12 (5%)	18 (7%)
Spinal type plain§	202 (78%)	214 (82%)	213 (81%)	203 (78%)
Bupivacaine dose, mg¶	12·0 (11·0–12·5)	12·5 (11·0–12·5)	12·5 (11·0–12·5)	12·5 (11·0–12·5)
Sufentanil administrated for participants in general anaesthesia (planned or converted from spinal)	54/67 (81%)	48/61 (79%)	53/60 (88%)	61/76 (80%)
Sufentanil dose, µg‖	22·5 (19·0–27·3)	22·8 (20·0–26·4)	22·5 (20·0–26·9)	25·0 (20·0–27·0)
Blood loss, mL**	300 (200–443)	300 (200–440)	250 (175–400)	300 (200–494)
Ondansetron 4 mg administrated††	252 (98%)	254 (97%)	251 (96%)	250 (96%)
Perioperative local infiltration analgesia††	0 %	0%	0%	1 (<1%)

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Risks of serious adverse events associated with non-steroidal anti-inflammatory drugs in gastrointestinal surgery. A protocol for a systematic review with meta-analysis and trial sequential analysis

Shaheer Bukhari[1] | Morten Fiil Leth[1] | Christina Cleveland Westerdahl Laursen[1] | Mia Larsen[2] | Anders Schou Tornøe[3] | Janus C. Jakobsen[4,5] | Mathias Maagaard[1] | Ole Mathiesen[1,6]

S2 – Individual serious adverse events

Serious adverse events	Number of studies in meta-analysis	Events with NSAID	N NSAID	Events with control	N control	Effect (RR)	Lower 95% CI	Upper 95% CI	P-value
Urinary retention	10	15	345	47	344	0,4	0,2	0,81	0,011
Delayed gastric emptying	2	10	56	19	58	0,55	0,28	1,07	0,077
Ileus	3	9	170	20	162	0,42	0,12	1,49	0,177
Haemorrhage	9	13	346	5	335	1,8	0,77	4,22	0,178
Deep vein thrombosis	1	0	18	2	17	0,19	0,01	3,67	0,271
Complete heart block	2	0	143	2	134	0,31	0,03	2,97	0,311
Hypoxemia	1	3	29	1	30	3,1	0,34	28,14	0,314
Respiratory failure	2	0	96	2	92	0,32	0,03	3	0,317
Wound infection	3	1	131	4	127	0,42	0,07	2,43	0,333
Post-operative pancreatic fistula	2	9	56	14	58	0,67	0,3	1,52	0,337
Death	1	0	18	1	17	0,32	0,01	7,24	0,47
Re-operation	2	3	39	1	40	2,14	0,26	17,54	0,477
Wound dehiscence	1	1	27	0	28	3,11	0,13	73,1	0,481
Hypoglycemia	1	0	27	1	28	0,34	0,01	8,12	0,509
Paranasal sinus neoplasm	1	0	27	1	28	0,34	0,01	8,12	0,509
Renal failure	1	1	20	0	19	2,85	0,12	65,93	0,513
Anastomotic leak	4	9	239	6	226	1,38	0,47	4,03	0,554
Cellulitis	1	1	27	2	28	0,52	0,05	5,39	0,582
ICU re-admission	1	1	21	2	23	0,55	0,05	5,61	0,612
Bile leakage	1	4	25	3	25	1,33	0,33	5,36	0,685
Atrial fibrillation	2	3	143	2	134	1,39	0,23	8,43	0,722

22 RCT, 1622 pt

SAE:

RR 0.78, 95% CI 0.51-1.19, p=0.24

Konklusion:

Manglende information til at drage sikre konklusioner.

J Am Coll Surg. 2021 May ; 232(5): 765–790.e1. doi:10.1016/j.jamcollsurg.2021.01.005.

A Systematic Review and Meta-Analysis of the Association between Non-Steroidal Anti-Inflammatory Drugs and Surgical Bleeding in the Perioperative Period

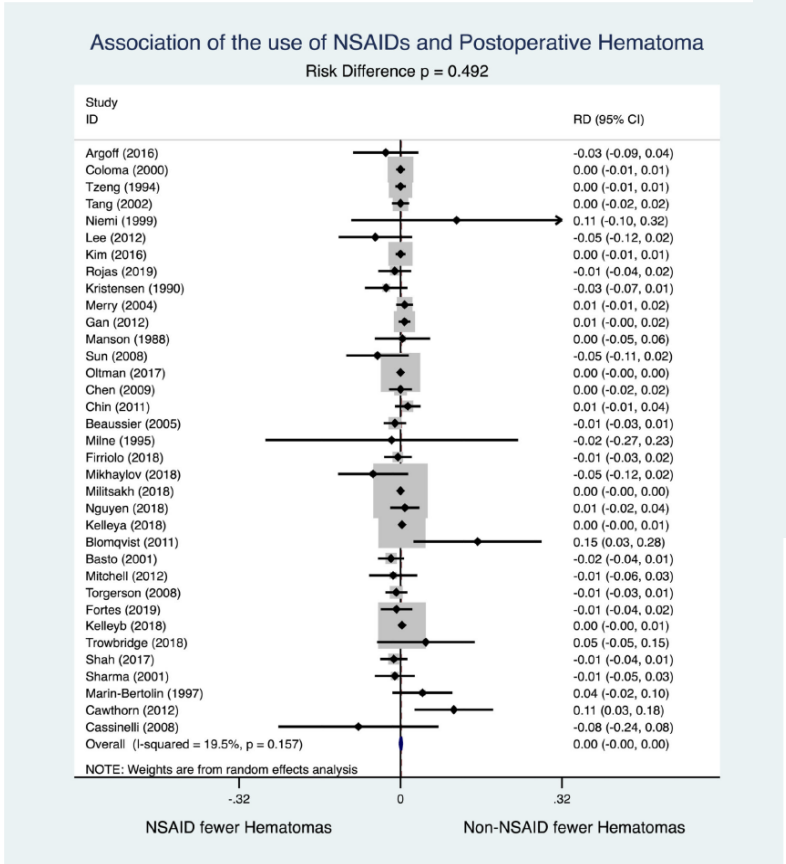
Tasce Bongiovanni, MD MPP[1], Elizabeth Lancaster, MD[1], Yeranui Ledesma, MD[1], Evans Whitaker, MD MLIS[2], Michael A Steinman, MD[3], Isabel Elaine Allen, PhD[4], Andrew Auerbach, MD, MPH[5], Liza Wick, MD FACS[1]

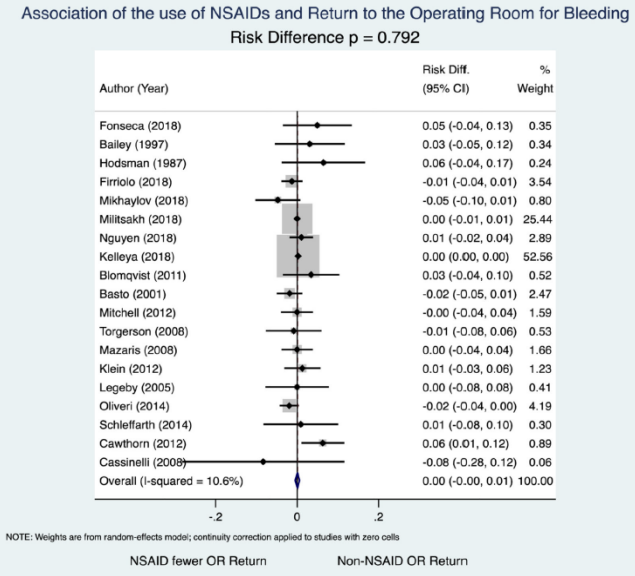
74 studier, > 151,000 pt
- 41 RCT
- 27 cohort
- 6 case-control

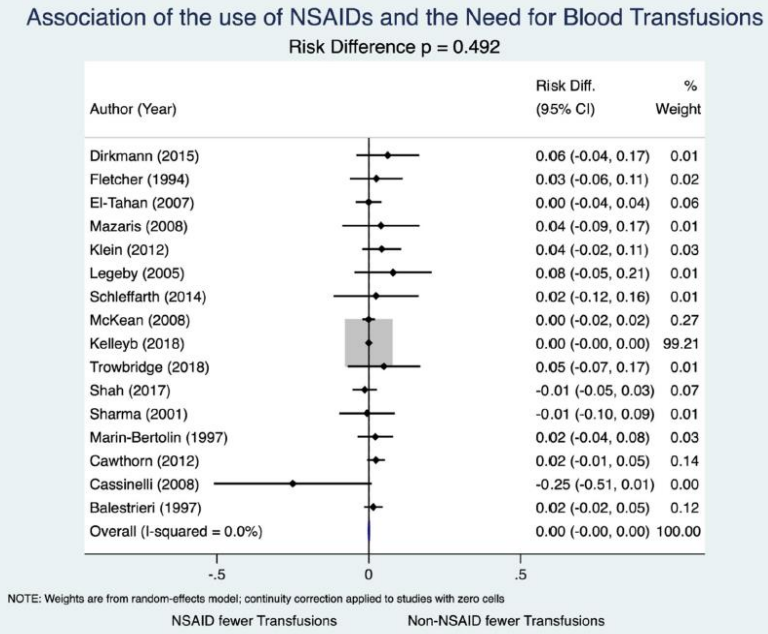
Hyppigste NSAID:
- Ketorolac
- Diclofenac
- Ibuprofen

Mange typer kirurgi

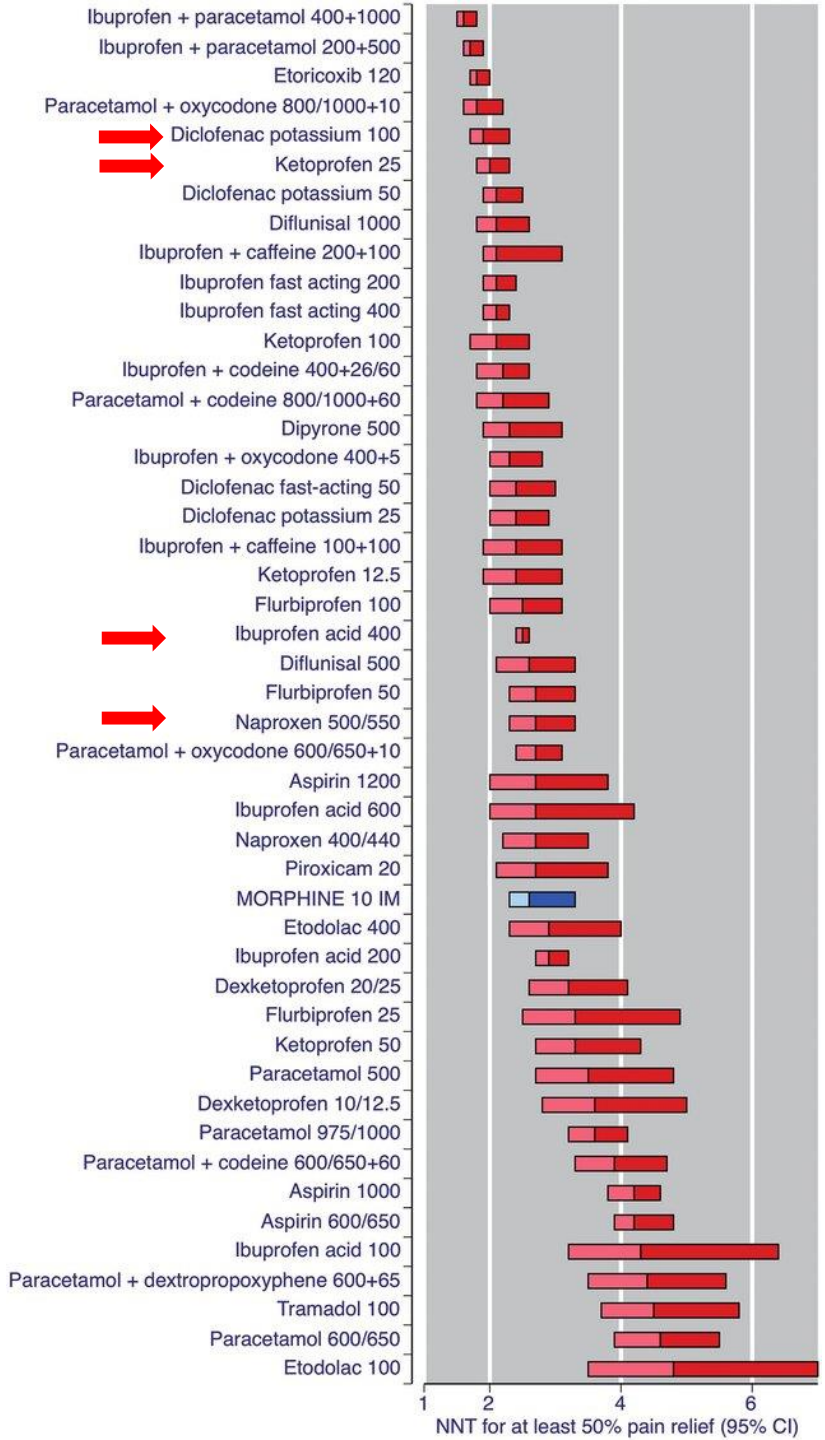
Konklusion: Ingen effekt af NSAID på perioperativ blødning







Cochrane:
Single dose oral analgesics for acute postoperative pain in adults (Review) Moore RA, Derry S, McQuay HJ, Wiffen PJ



Drug	Dose (mg)	Number of		At least 50% maximum pain relief over 4 - 6 hours						Susceptibility to publication bias
				Number with outcome/total		Percent with outcome		Risk ratio (95% CI)	NNT (95% CI)	
		Studies	Participants	Active	Placebo	Active	Placebo			
Dextropropoxyphene	65	6	440	85/214	60/226	40	27	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)	131
Diflunisal	250	3	195	49/98	16/97	47	16	2.9 (1.8 to 4.6)	3.3 (2.3 to 5.5)	396
Diclofenac fast-acting	25	2	325	36/165	4/160	22	3	8.7 (3.2 to 24)	5.2 (3.8 to 8.0)	325
Diclofenac sodium	50	2	313	58/193	18/120	30	15	2.0 (1.3 to 3.3)	6.6 (4.1 to 17)	161
Dihydrocodeine	30	3	194	31/97	19/97	32	20	1.6 (1.01 to 2.5)	8.1 (4.1 to 540)	46
Etodolac	50	4	360	44/154	34/206	29	17	1.7 (1.1 to 2.6)	8.3 (4.8 to 30)	74
Gabapentin	250	3	327	26/177	8/150	15	5	2.5 (1.2 to 5.0)	11 (6.4 to 35)	NNT above 10
Ibuprofen	50	3	316	50/159	16/157	31	10	3.2 (1.9 to 5.1)	4.7 (3.3 to 8.0)	356
Mefenamic acid	500	2	256	60/126	29/130	48	22	2.1 (1.5 to 3.1)	4.0 (2.7 to 7.1)	384
Naproxen	200/220	2	202	54/120	13/82	45	16	2.9 (1.6 to 5.1)	3.4 (2.4 to 5.8)	392
Oxycodone	15	3	228	61/113	37/115	54	32	1.7 (1.2 to 2.3)	4.6 (2.9 to 11)	268
Paracetamol + codeine	300+30	6	690	123/379	56/311	32	18	1.9 (1.4 to 2.5)	6.9 (4.8 to 12)	310
Paracetamol + oxycodone	325+5	3	388	60/221	14/167	27	8	3.6 (2.1 to 6.3)	5.4 (3.9 to 8.8)	331

Table 2

Drug and dose	Pain model	Trials	N	EER	CER	Relative benefit	NNT
Aspirin 600/650 mg	Dental pain	46	3635	35 (33–37)	14 (12–15)	2.5 (2.2–2.8)	4.7 (4.2–5.4)
Aspirin 600/650 mg	Postsurgical pain	22	1427	47 (43–50)	20 (18–24)	2.3 (1.9–2.7)	3.9 (3.3–4.7)
Paracetamol 600/650 mg	Dental pain	10	1265	36 (32–39)	12 (9–15)	2.9 (2.3–3.7)	4.2 (3.6–5.2)
Paracetamol 600/650 mg	Postsurgical pain	9	621	41 (36–47)	23 (18–28)	1.9 (1.5–2.4)	5.5 (3.9–9.1)
Paracetamol 975/1000 mg	Dental pain	10	1038	37 (33–41)	9 (7–12)	3.7 (2.7–5.1)	3.7 (3.1–4.7)
Paracetamol 1000 mg	Postsurgical pain	15	1721	51 (48–55)	26 (22–29)	2.2 (1.9–2.5)	3.9 (3.3–4.7)
Ibuprofen 400 mg	Dental pain	36	3402	56 (54–59)	12 (10–14)	5.2 (4.1–6.6)	2.2 (2.1–2.4)
Ibuprofen 400 mg	Postsurgical pain	13	1301	55 (52–59)	21 (18–25)	3.7 (2.6–5.1)	3.0 (2.6–3.4)

Statistical differences between absolute values were assessed with the Mann-Whitney U test, for relative risk a lack of overlap of confidence intervals, and for NNT by the z test. Shaded areas indicate statistically significant differences in outcome between models.

KJA
Korean Journal of Anesthesiology

Clinical Research Article

Korean J Anesthesiol 2023;76(6):597-616
https://doi.org/10.4097/kja.23014
pISSN 2005-6419 • eISSN 2005-7563

Comparison of different nonsteroidal anti-inflammatory drugs for cesarean section: a systematic review and network meta-analysis

Iona Murdoch[1], Anthony L Carver[1], Pervez Sultan[2], James E O'Carroll[2], Lindsay Blake[3], Brendan Carvalho[2], Desire N. Onwochei[1,4], Neel Desai[1,4]

[1]Department of Anesthesia, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [2]Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA, [3]University of Arkansas for Medical Sciences Library, Little Rock, AR, USA, [4]King's College London, London, United Kingdom

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Metode

- Præ-registreret - PROSPERO
- Metodemæssigt OK
- Inklusion:
  - RCT i CS patienter
  - NSAID vs control / andet NSAID
  - Elektiv / emergency trial
  - GA / SA / EPI
- 1. outcome:
  - Morfinforbrug, MID 10 mg
- 2. outcomes:
  - Pain, opioid-relateret AE, QoR-15, LOS

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Resultater

- 47 RCT
- 4 low RoB
- Elektiv (30), elektiv/akut (6), ikke defineret (11)
- Spinal (27), Comb. S-Epi (2), EPI (3), GA (11)
- Generelt: GRADE low to very low certainty of evidence
- Kun et studie med Ibuprofen

Primære outcome: 18 RCT med 1228 pt

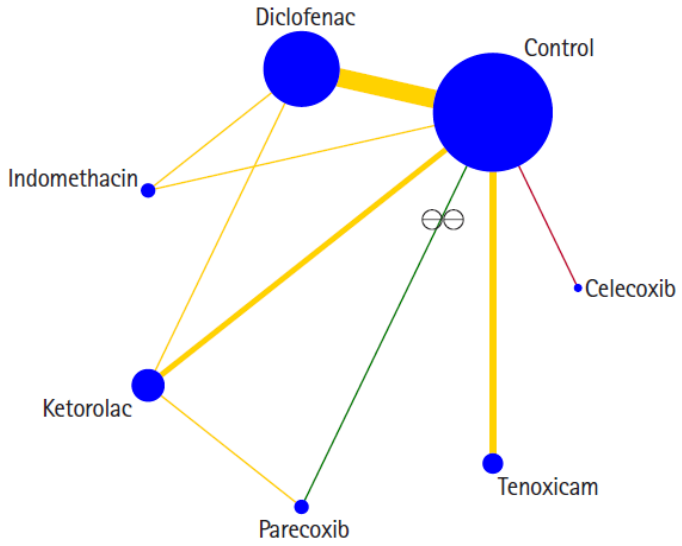


Fig. 3. Network plot in regard to the need for cumulative intravenous morphine equivalent consumption at 24 h. Each intervention is depicted by a circle that is proportional in size to the number of patients who were randomized to that intervention. Connecting lines between the circles indicate the direct comparisons of interventions, their width proportional to the number of trials evaluating the comparison, and their color representing the average risk of bias. Green: low risk, yellow: some concerns, red: high risk.

Table 2. Network League Table for All the Interventions in regard to Cumulative Intravenous Morphine Equivalent Consumption at 24 h

Celecoxib						
−14.21 (−36.00, 7.58)	Control					
5.66 (−17.31, 28.64)	19.87 (12.56, 27.18)*	Diclofenac				
7.07 (−21.96, 36.10)	21.28 (2.09, 40.47)*	1.41 (−17.78, 20.59)	Indomethacin			
−1.68 (−26.32, 22.96)	12.53 (1.00, 24.05)*	−7.34 (−20.34, 5.65)	−8.75 (−30.94, 13.44)	Ketorolac		
−6.12 (−33.53, 21.30)	8.09 (−8.57, 24.75)	−11.78 (−29.74, 6.18)	−13.19 (−38.51, 12.14)	−4.44 (−21.26, 12.39)	Parecoxib	
0.46 (−24.86, 25.78)	14.67 (1.74, 27.59)*	-5.20 (−20.05, 9.64)	−6.61 (−29.75, 16.53)	2.14 (−15.18, 19.46)	6.57 (−14.51, 27.66)	Tenoxicam

Estimates are presented as mean differences with 95% CI in parentheses. Mean differences below 0 favor the column intervention and mean differences above 0 favor the row intervention. *Interventions which are significantly different since the 95% CI does not include 0.

Konklusion

- Diclofenac, indomethacin, ketorolac, tenoxicam vs. placebo reducerer 24t morfinforbrug
- GRADE + CI:
  - Ingen sikker forskel mellem individuelle NSAIDs på opioid forbrug
  - Indomethacin måske bedst….
  - OBS Indometacin kun på udleveringstilladelse i DK
- Få studier med low risk of bias
- Paracetamol kun givet i få studier
- Ibuprofen få studier
- Konclusion:
  - Måske minimal forskel mlm NSAIDs i reviewet
  - Non-specific måske mest effektive

Digestive Diseases and Sciences (2023) 68:1975–1982
https://doi.org/10.1007/s10620-022-07788-y

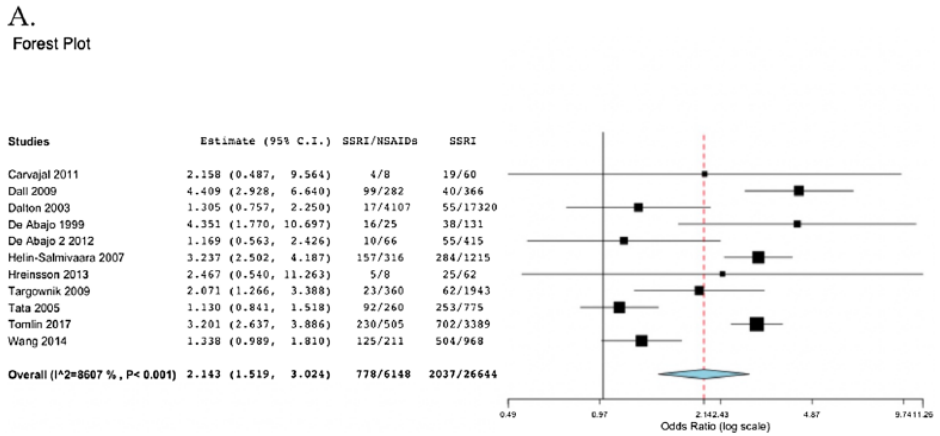
ORIGINAL ARTICLE

Risk of Gastrointestinal Bleeding with Concurrent Use of NSAID and SSRI: A Systematic Review and Network Meta-Analysis

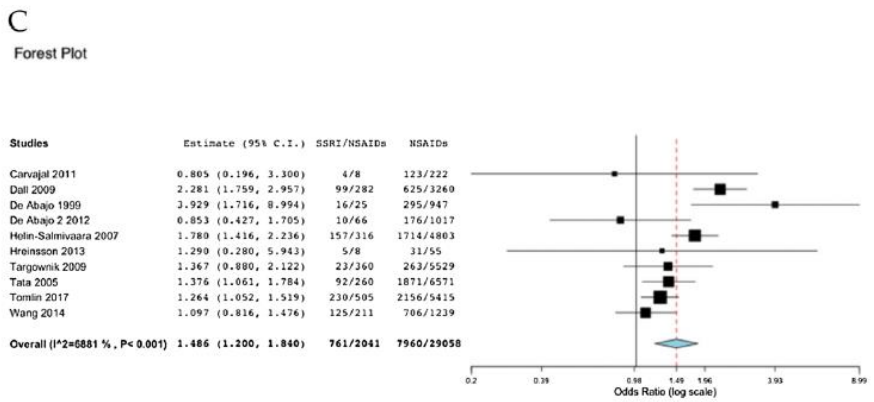
Hossein Haghbin[1] · Nuruddinkhodja Zakirkhodjaev[2] · Faiza Fatima Husain[3] · Wade Lee-Smith[4] · Muhammad Aziz[5]

15 kohorte studier med > 82.000 pt

SSRI+NSAID vs SSRI



SSRI+NSAID vs NSAID



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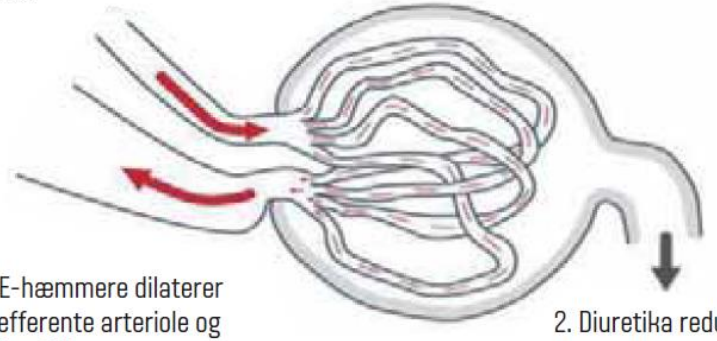
Tripple whammy

Figur 1. Effekten af 'the triple whammy' på nyrefunktionen

Triple Whammy effekt

NSAID: f.eks.
Ibuprofen
Diclofenac
Voltaren

3. NSAID kontraherer den afferente arterlole og nedsætter dermed blodgennemstrømningen i glomerulus



ACE-hæmmer:
f.eks. Ramipril
AT-II antagonist:
f.eks. Losartan

1. ACE-hæmmere dilaterer den efferente arteriole og sænker GFR

2. Diuretika reducerer plasmavolumen og GFR

Diuretika: f.eks.
Centyl
Thiazid
Furix

OBS! ved pt i enkeltstofsbehandling:
ACE-I/AT-II: NSAID kan nedsætte anti-hypertensiv effekt og påvirke nyrerne
Diuretikum: NSAID kan nedsætte diuretisk effekt og påvirke nyrerne

Kilde: NordKAP Lægemiddelenhedens nyhedsbrev 2017

NSAID + NOAC

- Pro.medicin.dk
- Forsigtighed tilrådes ved:
  - Samtidig antikoagulationsbehandling pga. øget blødningsrisiko (nedsat trombocytaggregation, øget ventrikelslimhindeirritation og plasmaproteinbinding, som medfører øget antikoagulanskoncentration i blodet).
  - Ved samtidig ASA- eller warfarinbehandling er risikoen for gastro-intestinal blødning ens for COX-2-hæmmere og uspecifikke NSAID.

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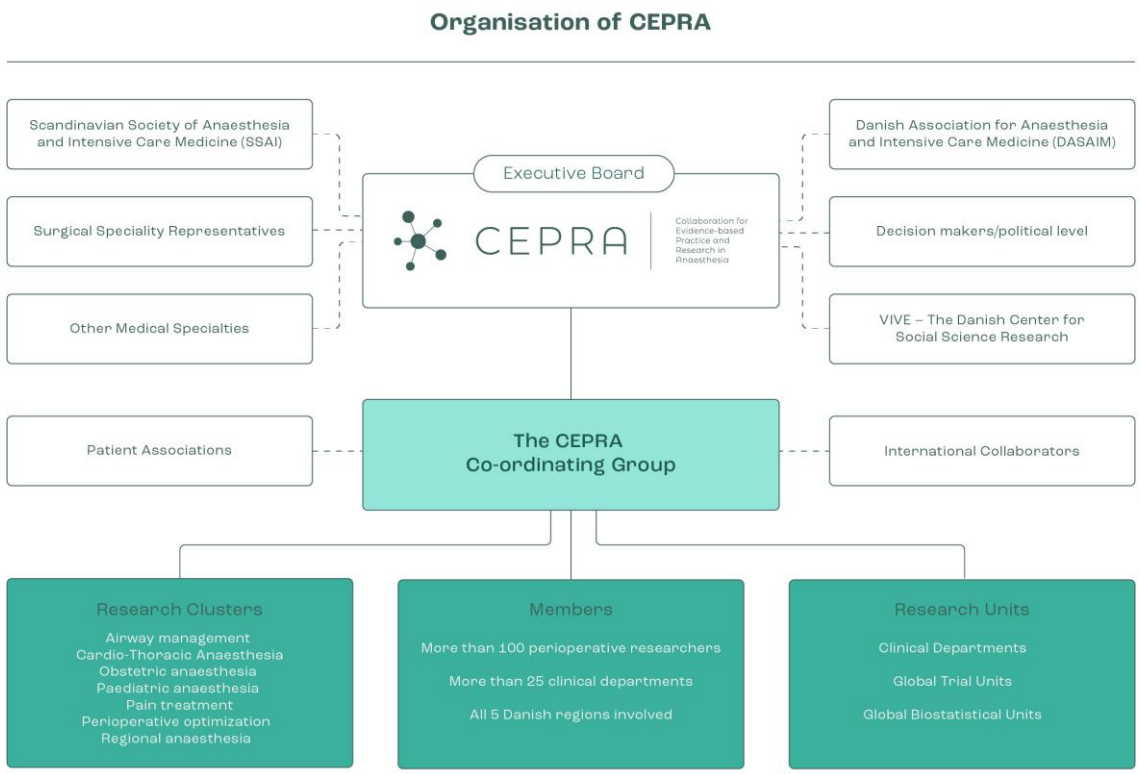
Safety of ibuprofen after major orthopaedic surgeries

The PERISAFE randomized clinical multicentre trial

Collaboration of Evidencebased Practice and Research in Anaesthesia (CEPRA)

CEPRA

Collaboration of Evidencebased Practice and Research in Anaesthesia (CEPRA)



- **Smerte**
  - **PERISAFE 1+2**
  - **PPA (Personalized Patient Analgesia)**
  - **OPI•AID**
- **Obstetrisk**
  - **MOTHER trial**
- **Regional blokade**
  - **The BLOCK trial**
- **Luftvej**
  - **ROC-VIDEO trial**
- **Perioperativ optimering**
  - **DAPPER Trial**
- **Pædiatrisk**
  - **INDEX trial**
- **CardioThorasic Anaesthesa**
  - **DEXA-VATS**

CEPRA

MOTHER trial

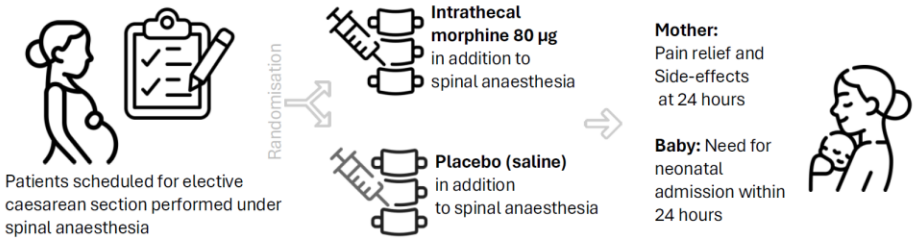
Effect of low-dose intrathecal morphine in addition to multimodal postoperative pain management in patients undergoing elective caesarean *section*

– a randomised, clinical, placebo-controlled, multicentre trial

Severe postoperative pain is experienced by 45% of patients undergoing caesarean delivery. Intrathecal morphine is praised for its long-lasting pain-relief but has several side-effects.

Sufficient pain-relief and a fast recovery is important for both mother and baby. Despite wide-spread use, the practice is based on a low level of evidence, and the balance between pain-relief and possible adverse effects remains poorly described.

The purpose of this trial is to optimise postoperative pain management for patients undergoing elective caesarean section



Patients scheduled for elective caesarean section performed under spinal anaesthesia

Primary maternal outcomes

- Level of pain (NRS 0-10) during sitting up 24 hours after administration.
- Morphine associated adverse events within 24 hours (dichotomic composite: nausea, vomiting, dizziness, itching, or urine-retention).

Secondary outcomes

- Postpartum opioid use during hospitalisation (oral morphine mg equivalents) within 24 hours.
- The ability to independent mobilisation (yes/no) at 24 hours after surgery.
- The ability to independently nurse baby/neonatal at 24 hours after surgery.
- Level of pain at movement (NRS 0-10) at 6, 12, 18, 24 and 48 hours post-surgery, assessed using questionnaire by SMS to mothers' phone at relevant time points.
- Spinal anaesthesia related adverse events at caesarean section.

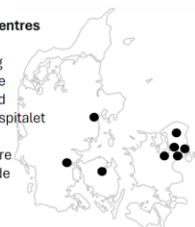
Sample size

We plan to include 1,300 patients

based on an adverse events baseline incidence of 36% without morphine and a relative risk increase in adverse events of 20% and power of 80%. We correct statistically for having two primary outcomes by using alpha of 2.5%. We reach a power of 99.9% for the co-primary outcome of pain score with an estimated mean NRS of 4.5, standard deviation of 2.1 and relevant mean difference of 1.0.

Perspective

The MOTHER-trial will clarify the balance between pain-relief and side-effects of intrathecal morphine. The results will serve as guidance in providing a personal tailored treatment of postoperative pain. Women are culturally expected to feel pain at delivery, but we aim to improve the care of women giving birth by caesarean section, and hopefully this will improve the experience of early motherhood and aid mother-child bonding.



Trial Centres
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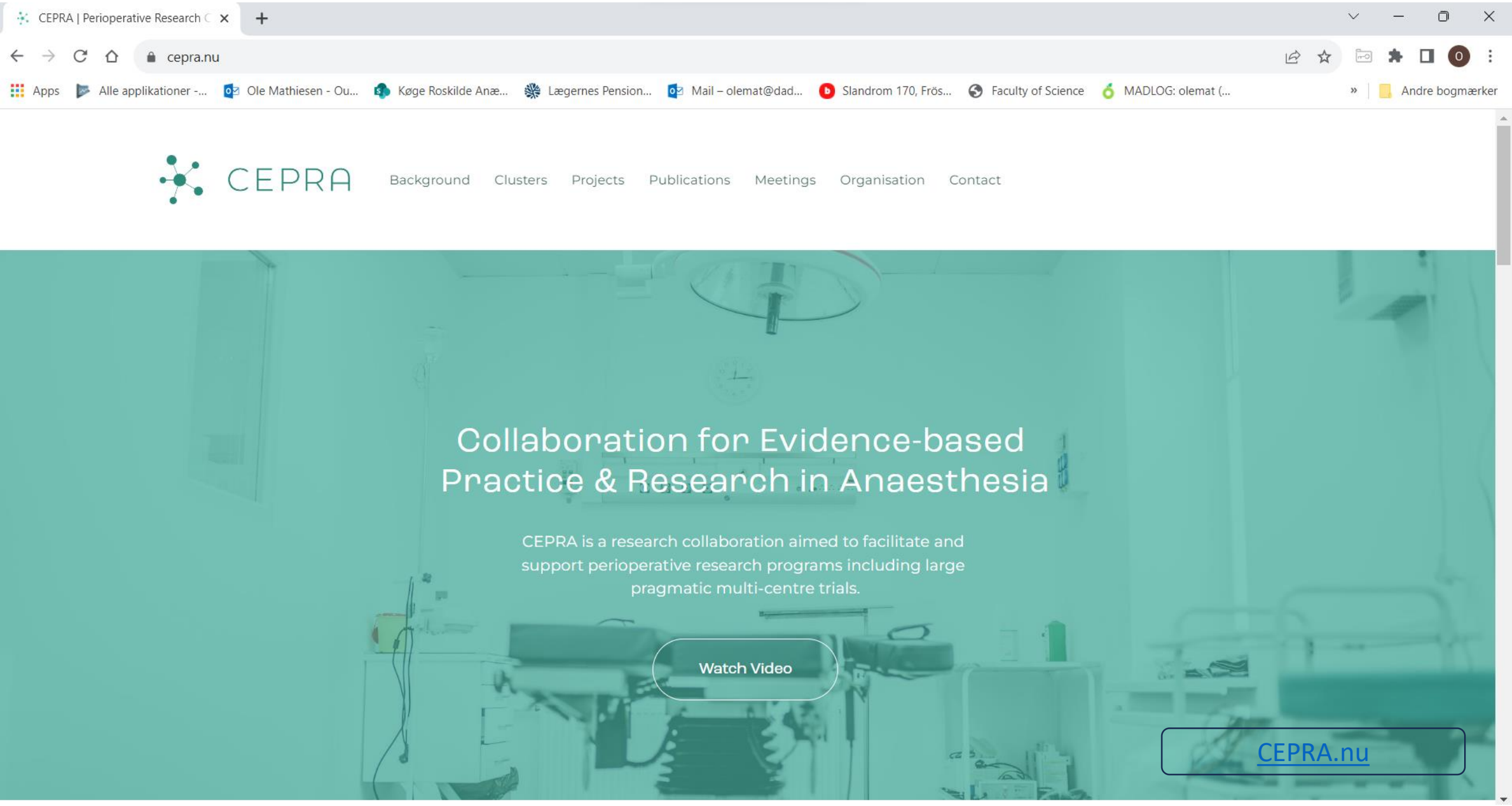
Kolding
Odense
Hillerød
Rigshospitalet
Herlev
Hvidovre
Roskilde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Any
Questions