Clinical trials in paediatric pain treatment

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Outline of the lecture

What do we have in paediatric pain ?

Importance of age in paediatric trials

General aspects of trial methodology

Trials in chronic pain

Trials in acute pain: A systematic review on placebo controlled trials on acute postoperative pain

What do we still need in area of paediatric analgesic trials ?

What do we have in paediatric pain treatment?

Data on epidemiology of paediatric pain

Data on pharmacokinetics of opioids and NSAIDs in different age groups

Lot of short studies on acute postoperative pain, often active vs active, no placebo controls

Variety of (validated) pain measurement tools

Data on psychology of paediatric pain

Problems of paediatric analgesic trials

TABLE 1. *Problems with pediatric analgesic trials*

Problem	Possible solutions
Difficulties with informed consent	1. Parental informed consent (patient assent whenever possible) 2. Age-appropriate explanations
Age-related differences in pharmacokinetics and pharmacodynamics	1. Studies stratified for different age groups 2. Newborn animal testing for new drug classes to detect specific toxicities
Difficulties with pain assessment	1. VAS for ages 7 and above 2. Novel self-report scales for ages 3–7 (Faces, ACCS, Oucher, Poker Chip) 3. Behavioral scales for ages 3 and under 4. Correlation of behavioral and self-report measures in the 3–9-year-old age groups
Small population sizes	1. Multicenter trials 2. Initial studies on relatively large and uniform postoperative patients
Rapidly changing intensity of cancer pain	1. Study designs with short time courses 2. Multicenter trials
Difficulty with blood sampling Distress with venipuncture Small blood volume Difficulty finding veins Difficulty with repeated sampling from peripheral "heparin-locks"	1. Enrollment among patients with central lines required for surgery, cancer therapy, or intensive care 2. Placement of venous or arterial lines while patients are receiving general anethesia 3. Development of micromethods for plasma drug assay

Berde CB 1991

Age affects many aspects of paediatric trials

Experience and expression of pain is affected by

- cognitive and linguistic development
- previous experience of pain, learning, mood
- environmental influences: separation from parents, unfamiliar surroundings and staff
- understanding of illness and medical procedures

Validity and choice of pain measurement tools

McGrath and Unruh 1999

Relevant outcomes

Feasible methods/routes of pain relief

Change of pharmacokinetics by age

- body compartments
- plasma protein binding
- renal filtration and excretion of drugs and their metabolites
- metabolic rate

Olkkola KT et al. 1995

Validity of trial design

Randomization: non randomisation overestimates treatment effect by 41%

Blinding

Group size: small trials overestimate effect by 30%

- “Size is everything when showing equivalence”
- “Smaller the difference – larger the trial”

Sensitivity of trial design

Moore RA et al. 1998, Moore A et al. 2003

Sensitivity of trial design

Depends on

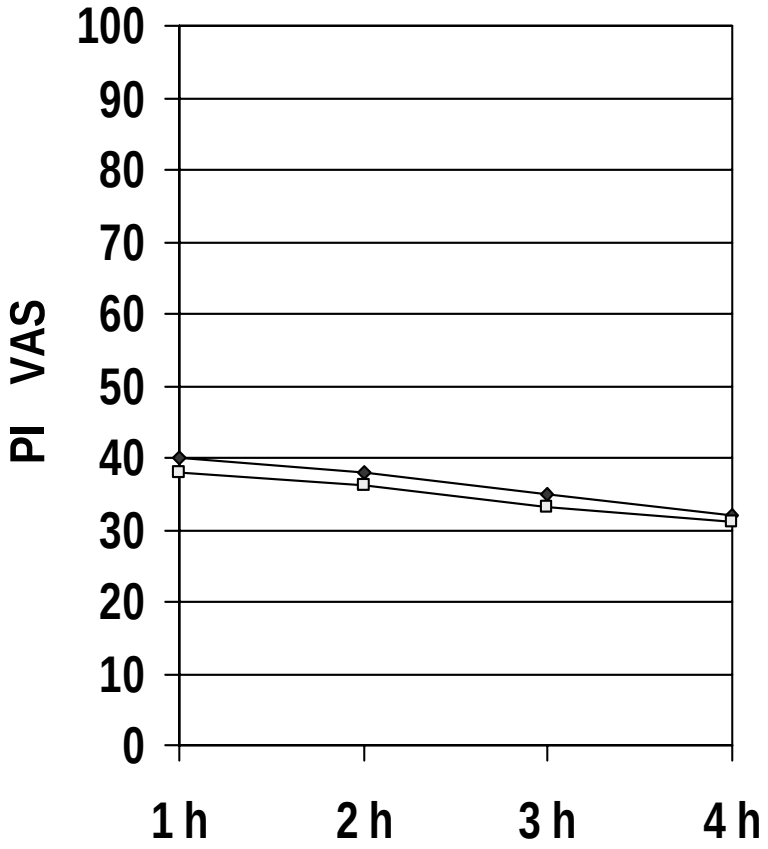
- effect size
- pain intensity

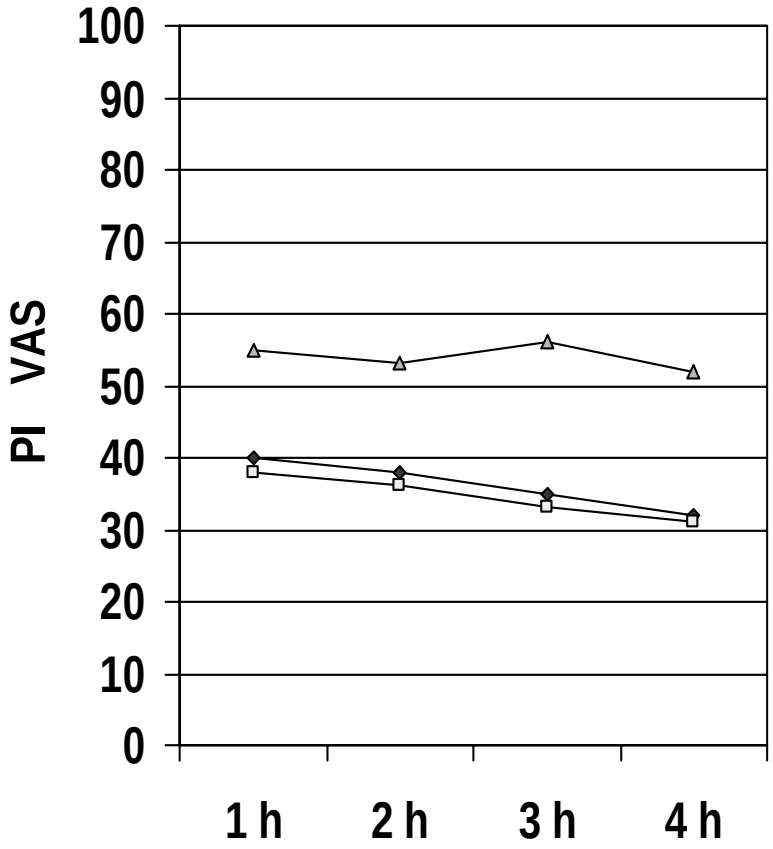
Can be assumed if a difference is found between study analgesics

In case of equal effect: placebo, active control or dose-response is needed

Kalso E 1996, 2002, Moore A et al. 2003, Bjune K 1996

Equal effect





Chronic pain in children

- headache/migraine
- recurrent abdominal pain
- musculoskeletal pain

- rheumatoid arthritis
- cancer pain
- sickle cell disease
- neuropathic pain, CRPS

Perquin CW et al. 2000, McGrath and Finley 1999

Chronic pain in children

Very few studies on therapy compared with acute pain

In clinical practice pharmacological treatments used based on data extrapolated from adults

"Benign" conditions often treated with non-pharmacological methods

Small patient populations, outpatient settings, long enough follow ups

Trials on chronic pain in children

Migraine

- acute attacks: paracetamol, ibuprofen and sumatriptan
- some prophylactic agents

Juvenile RA: NSAIDs

Cancer pain: opioids

- only a few retrospective /open label studies (oral morphine, td fentanyl)

No data on anticonvulsants or antidepressants for pain

What can we learn from the placebo group of randomised controlled trials in paediatric postoperative pain?

A systematic review.

Katri Hamunen, Eija Kalso

Purpose of the study

Background

- Placebo-controlled RCT – gold standard of analgesic trials *(Moore A et al. 2003)*
- Use of placebo in paediatric trials controversial (*Schachtel and Thoden 1993; Anderson et al. 2001)*

To evaluate

- how placebos are used in RCTs on paediatric postoperative pain
- how this information can be used to improve research methodology

Methods

Systematic review on randomised controlled studies on systemic NSAIDs, paracetamol and opioids given for acute postoperative pain in children

Placebo group and N ≥ 10 per group

Medline, PreMedline, Cinahl, Cochrane Library upto April 2003

Data extraction using structured form

Analgesics used

Type of surgery

Methods of pain measurement

Duration of follow up

Postoperative pain outcomes used

Rescue analgesic and criteria used

Pain intensity in the placebo groups

Hierarchy of the postoperative outcomes

Time to first rescue analgesia dose

Need of rescue analgesia

- number of patients
- total dose or number of doses

Pain intensity

Sensitivity of trial design

Statistical difference found between placebo and active drug

- in time to rescue analgesia
- need of rescue analgesia
- pain intensity

Search results

2438 abstracts/titles evaluated online

↓

83 studies fulfilled inclusion criteria

↙ ↘

43 excluded

40 included

Reasons for exclusion

Adults mixed	10 studies
No postoperative pain outcome	8
Methodological problems	7
Not RCT	3
Other analgesics	3
No real placebo group	3
N < 10	2
Language	2
Other than systemic administration	2
Duplicate	1
Retrospective and duplicate	1
Not prospective placebo-controlled	1

40 studies included

1. Analgesics administered for established pain N = 2

2. Prophylactically administered analgesics, no other analgesics given N = 18

3. Prophylactically administered analgesics, in addition other analgesics administered N = 20

Results

40 studies, 3519 patients

Median group size 28 (range 10 - 84)

36/40 double-blind, 21 double-dummy

Duration of follow up

< 24 h	21 studies: median 120 (60-480) min
24 - 36 h	16 studies: median 1440 (1440-2160) min
> 36 h	3 studies

Analgesics studied

7 NSAIDs

Ketoprofen, ketorolac, diclofenac, ibuprofen, indomethacin, flubiprofen, rofecoxib

Paracetamol, propacetamol

7 different opioid analgesics

Pethidine, papaveretum, fentanyl, tramadol, morphine, butorphanol, nalbuphine

Methods of pain measurement

Patient	4 studies (VAS, Oucher, VRS)
Observer	25 studies
Both	10 studies
Unclear	1

Multiple tools used in 14 studies

Postoperative outcomes used

Primary outcome named in **2**/40 studies

Need of rescue analgesia	36 studies
N of patients given rescue analgesia	34
N of rescue analgesic doses	11
Total dose of rescue analgesia	8
Pain intensity	34
Time to first rescue analgesia dose	15

Postoperative outcomes – cont.

Pain on activity	8
N of patients with pain	6
Pain relief	3
Global efficacy	2
Use of PCA	4

Need of rescue analgesia as an outcome

Used in 36 studies (N of patients, total dose, n of doses)

Criteria for administration of rescue analgesia

Reported	20/36 studies
No numerical criteria reported	12
PCA	4

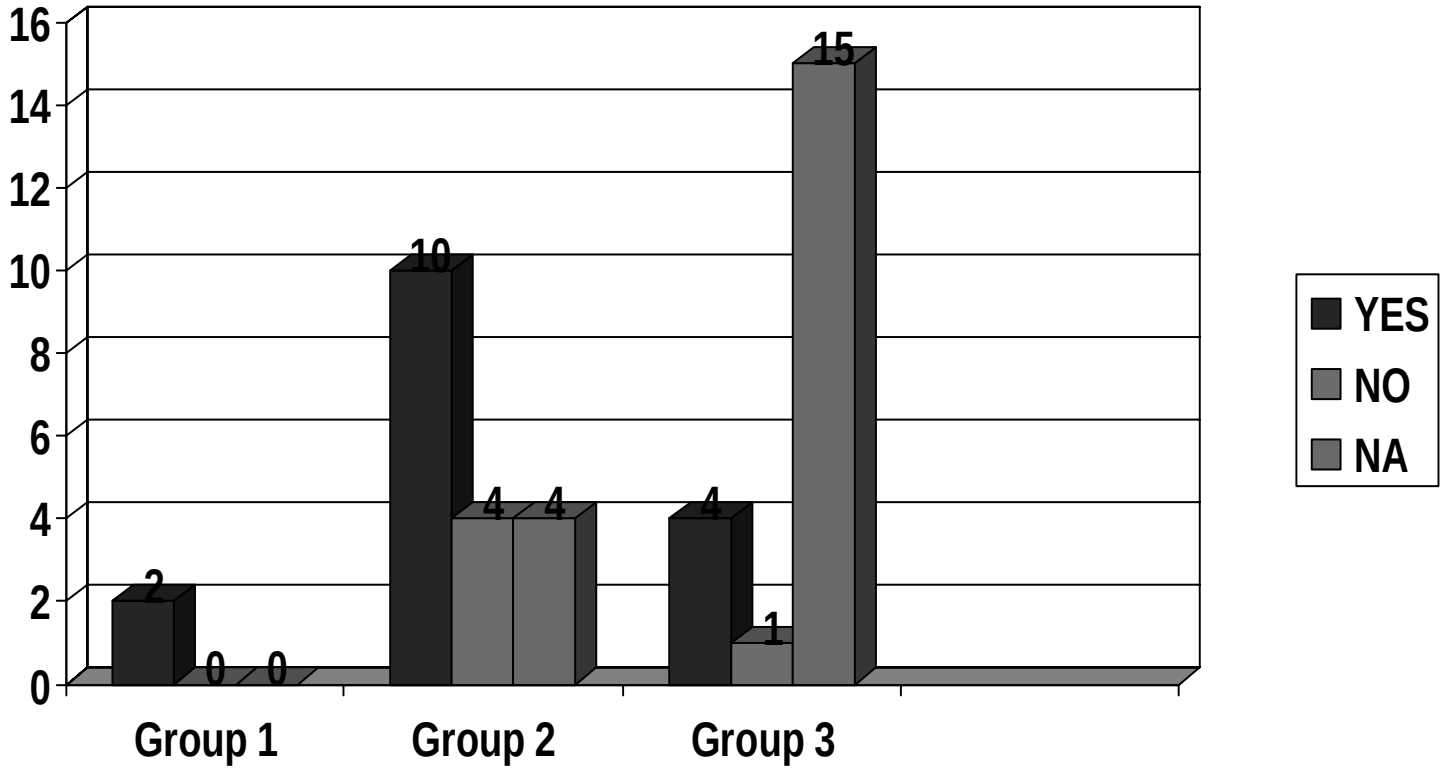
Criteria 20-77% of PI maximum, median 36,5 % (N=16)

Multiple criteria in 4 studies

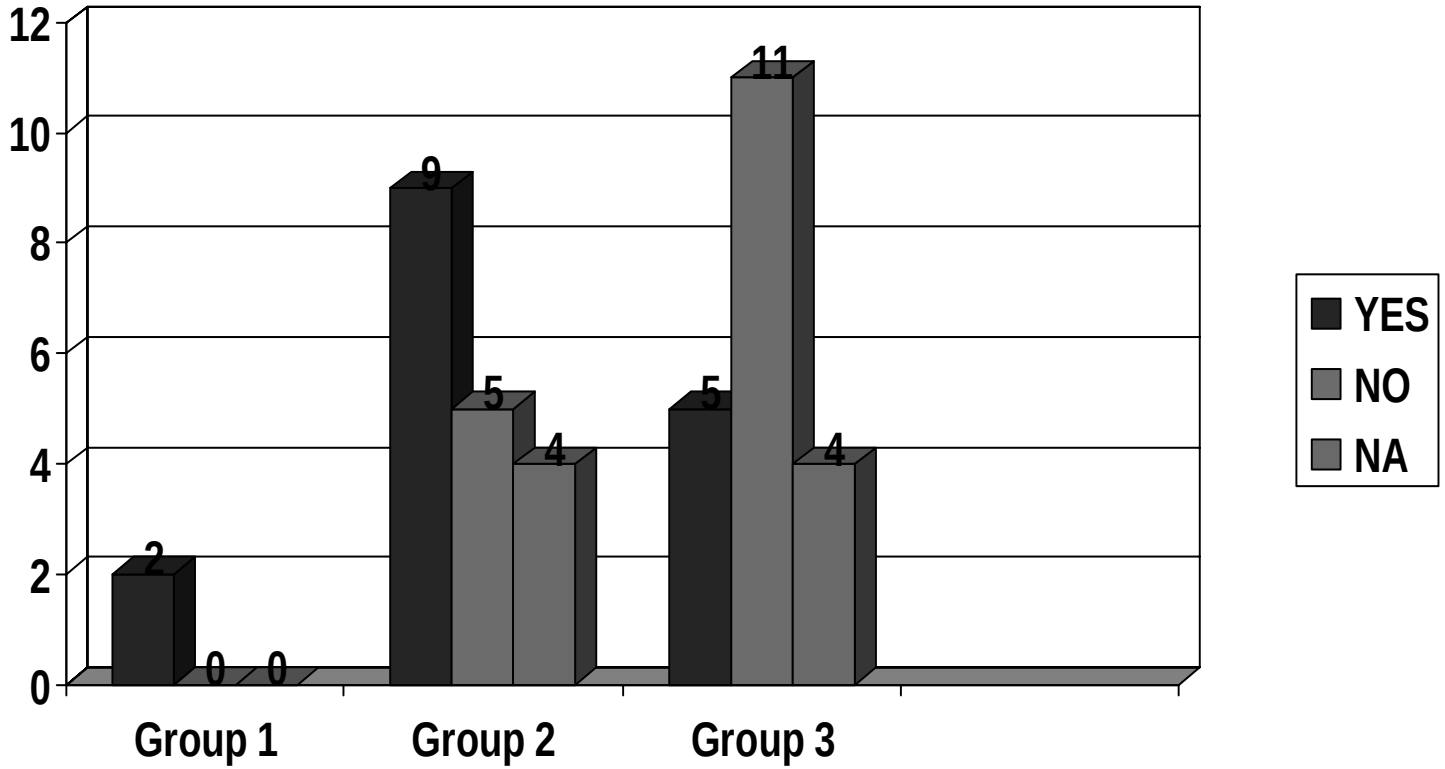
Rescue analgesic administered in 38/40 studies

named in 34/38 studies, opioid analgesic in 16 studies

Initial pain intensity ≥ 30% of maximum in placebo groups



Pain intensity ≥ 30% of maximum at least 50% of follow up in the placebo groups



Number of patients given rescue analgesia in "clean" placebo groups

Operation	Placebo	Active(s)	Follow up
Strabismus	75%	35-50%	1 h
	78%	67-72%	2 h
	93%	50-97%	8 h
T ± A	95%	96%	14 min
	73%	0%	1 h
	100%	50-85%	24 h
	84%	48-52%	24 h

Number of patients given rescue analgesia in "clean" placebo groups

Operation	Placebo	Active(s)	Follow up
BMT	21%	23-31%	1 h
	53%	7-20%	1 h
	76%	30-55%	1 h
	63%	40-48%	24 h
Dental	86%	19%	2 h
Appendic.	90%	50-55%	24 h

Number of patients given rescue analgesia in "clean" placebo groups

Operation	Placebo	Active(s)	Follow up
Various	66%	34%	12 min
	90%	23-63%	2 h*
	93%	43-44%	2 h
	80%	17-63%	24 h*
	98%	86%	24 h
	81%	64%	upto 3 days

Propacetamol 30 mg/kg iv vs placebo

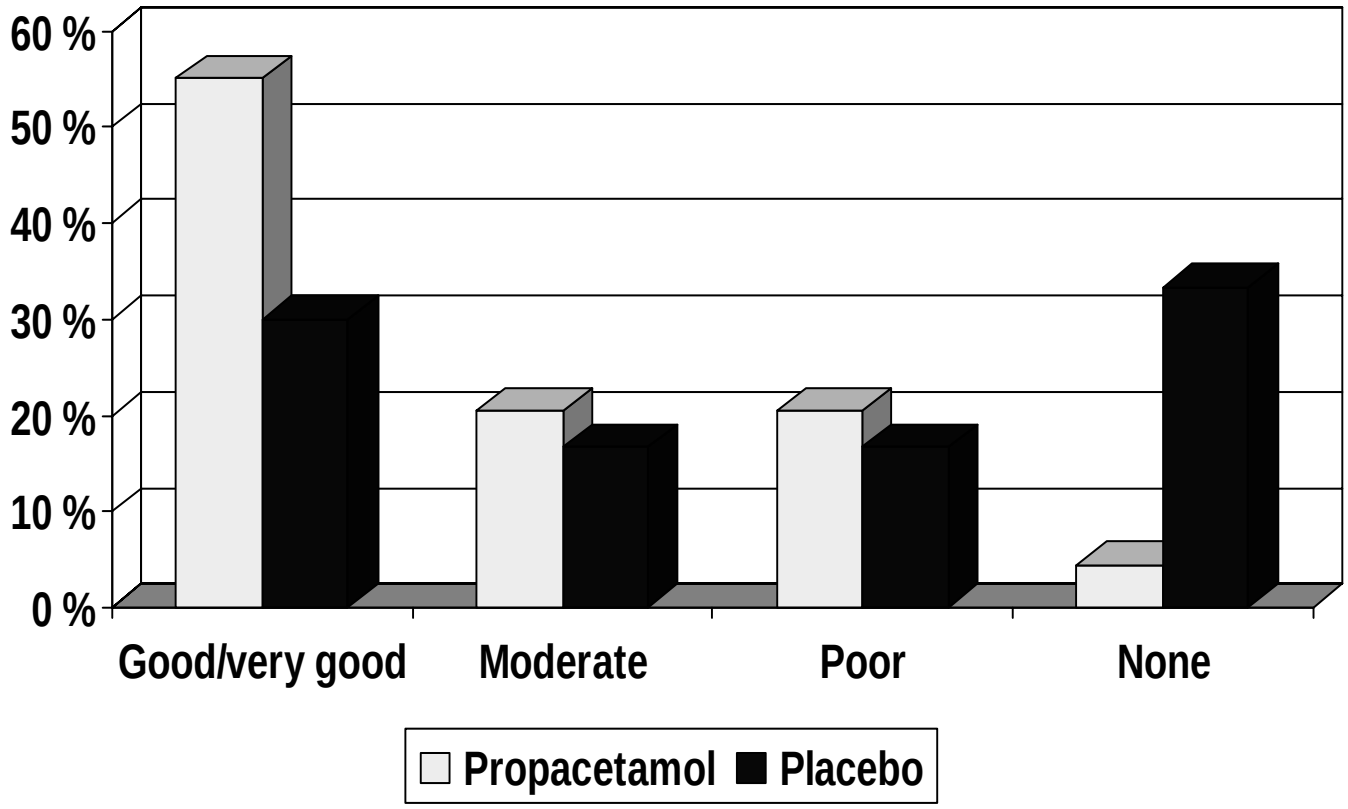
Granry et al. 1997

- orthopaedic surgery, 9 yrs, N= 44 + 43
- pain 3-5/5 before study analgesics administered

Time to first dose of rescue analgesia

propacetamol	156 (33-285) min
placebo	118 (33-285) min ($p < 0.01$)

Pain relief


60 %
50 %
40 %
30 %
20 %
10 %
0 %
Good/very good
Moderate
Poor
None
Propacetamol
Placebo

Time to first dose of rescue analgesia after placebo

Tonsillectomy	10 min (mean)
Appendicectomy	65 min
Tonsillectomy	5 min (median)
Various	12.5 min

Trial sensitivity

Group 2 (prophylactic, no additional analgesics)

Difference between study groups was found

Time to first rescue analgesia dose	5 studies
Need of rescue analgesia	15
Pain intensity	8

Conclusions

In most studies

- analgesics were administered in a prophylactic manner and therefore the actual placebo effect could not be evaluated
- the placebo group served a control of normal postoperative outcome

Children experience significant pain after various types of surgery and these models can be used to study analgesics

Variable trial designs and methods complicate comparisons between trials

- for clinical purposes
- for further methodological evaluation

Sensitivity of trial design varied by outcome used (time to rescue, need of rescue, PI)

Need of rescue analgesia

- was the most common outcome used
- with prophylactic administration of study analgesics showed more differences than other outcomes

Criteria for rescue analgesia

- not always reported
- varied greatly
- **what is the appropriate level ?**

When using prophylactic administration of study drugs trial design should

- include a large enough number of patients
- primary outcome stated: time to rescue analgesia, criteria given should be given
- secondary outcome: number of patients given rescue analgesia (adequate follow up time) or pain intensity

Placebos can be used in paediatric analgesic studies to demonstrate internal sensitivity provided that

- informed consent (patient and/or parent) is obtained
- effective rescue analgesia is always available

Future challenges

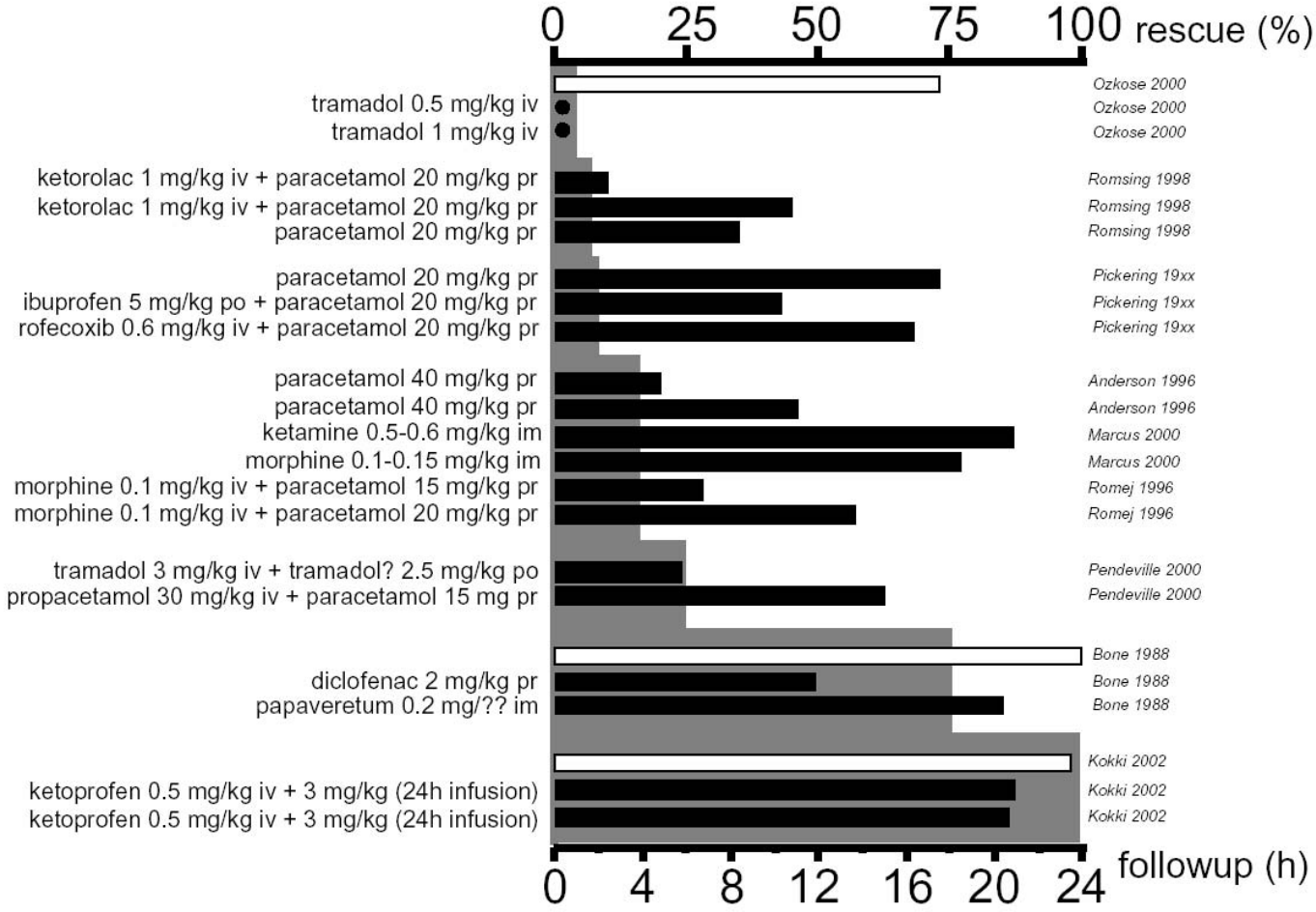
- to explore the placebo effect in children
- to develop more standardized trial methodology

Systematic review on analgesics given for pain following tonsillectomy in children

Katri Hamunen, Vesa K Kontinen

NSAIDs, paracetamol or opioids for pain after tonsillectomy in children

- 36 studies, methods as in the placebo review
- 34/36 prophylactic administration
- only 5/36 truly placebo controlled
- variable methodology as in the placebo review
- 16/36 sensitive trial design



Note variable follow ups and rescue criteria

What do we need in area of paediatric analgesic trials?

More standardized methodology

- clearly defined, clinically significant outcomes
- demonstration of sensitivity of trial design
- large enough group sizes
- standardized, age-appropriate measurement tools
- clinically and pharmacologically relevant follow up periods
- defined criteria for rescue analgesia

Data on clinically significant outcomes

- which are the best outcomes to study in acute/chronic pain states?
- what is clinically significant reduction in pain for children in acute/chronic pain?
- what is the appropriate criteria for rescue analgesia?

Longer follow up periods, studies at home following (day case) surgery

Data on placebo

- nature and magnitude of placebo effect in children of various age
- ethics of placebo in paediatric trials

Data on pharmacology of antidepressants and anticonvulsants in children

Data on long-term effects of analgesics on developing CNS

Trials in chronic pain states

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