Supplementary Online Content

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. *JAMA*. doi:10.1001/jama.2018.22039

Table of Contents

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Complete List of Inclusion and Exclusion Criteria

Inclusion criteria

Patients must meet all the following criteria to be suitable for inclusion in the trial:

- Scheduled for unilateral, primary THA
- Age > 18
- ASA 1-3.
- BMI > 18 and < 40
- Women in the fertile age must have negative urine HCG pregnancy test
- Patients who gave their written informed consent to participating in the trial after having fully understood the contents of the protocol and restrictions.

Exclusion criteria

Patients who meet one or more of the following criteria are not suitable for inclusion in this trial:

- Patients who cannot cooperate with the trial.
- Concomitant participation in another trial
- Patients who cannot understand or speak Danish.
- Daily use of strong opioids (tramadol and codein are accepted)
- Patients with allergy to the medicines used in the trial.
- Contraindications against NSAID or paracetamol, for example previous ulcer, heart failure, liver failure, or renal failure (eGRF < 60 ml/kg/1,73m2), known thrombocytopenia (<100 mia/L)
- Patients suffering from alcohol and/or drug abuse – based on the investigator's judgement.

eAppendix 2. Abstracts Written Before Breaking the Randomization Code

Group A = PCM+IBU; Group B = PCM; Group C = IBU; Group D = HS-PCM+IBU

ABSTRACT No 1: Group 1 is the control group for the SAE outcome

PAracetamol and NSAID in combination for postoperative analgesia after primary hip arthroplasty: The randomised, blinded, parallel 4-group PANSAID clinical trial

Importance: Multimodal postoperative analgesia is widely used but lacks direct evidence.

Objective: Investigate beneficial and harmful effects of 4 nonopioid analgesics.

Design: PANSAID is a randomized, blinded, placebo-controlled, four-group trial with 90 days follow-up.

Setting: Six Danish hospitals.

Participants: 556 patients with total hip arthroplasty from December 2015 to October 2017.

Intervention: Participants randomized to Group A paracetamol 1 g and ibuprofen 400 mg; Group B paracetamol 1 g and placebo; Group C ibuprofen 400 mg and placebo; or Group D paracetamol 0.5 g and ibuprofen 200 mg; orally, every six hours for 24 hours postoperatively, starting one hour before surgery.

Main outcomes: Two preplanned co-primary outcomes: 24-hours morphine consumption using patient-controlled analgesia in pairwise comparisons between the four groups; and proportion of patients with one or more serious adverse event (SAEs) within 90 days in groups A, C and D combined versus group B.

Results: 556 were analyzed (mean age, 67 years, 277 (50%) women). The median (interquartile range) 24-hour morphine consumption in group A, B, C, and D was 20 (12-40), 36 (24.5-52) mg, 26 (18-46), and 28 (18-46) respectively. The largest median difference was 16 mg (99.6%CI: 6.5 to 24, P<0.001) between group A and B. The difference was 8 mg (99.6%CI: -1 to 14, P=.0011) between group B and D and 6 mg (99.6%CI: -2 to 16, P=.0024) between group A and C. The differences between group A and D (8 mg (99.6%CI: -2 to 16, P=.0051)) and group B and C (10 mg (99.6%CI: -2 to 16, P=.0044)) were not statistically significant adjusted for multiple comparisons and two co-primary outcomes. There was no difference between groups C and D (2 mg (99.6%CI: -10 to 7, P=.81).

The proportion of patients with SAEs in the groups 2, 3, and 4 was 15% (97.5%CI: 12 to 20) and 14% (97.5%CI: 9 to 22) in group 1. The relative risk of SAE in the groups 2, 3, and 4 compared with group 1 was 1.07 (97.5%CI: 0.63 to 1.81, P=.79).

Conclusion and relevance: Group 3 compared with group 4 reduced morphine consumption more than the minimal important difference. Using ibuprofen the first postoperative day does not statistically significant increase the proportion of SAEs.

Trial registration: Clinicaltrials.gov identifier: NCT02571361

ABSTRACT No 2: Group 2 is the control group for the SAE outcome (after unblinding it became clear that this is the relevant abstract).

PAracetamol and NSAID in combination for postoperative analgesia after primary hip arthroplasty: The randomised, blinded, parallel 4-group PANSAID clinical trial

Importance: Multimodal postoperative analgesia is widely used but lacks direct evidence.

Objective: Investigate beneficial and harmful effects of 4 nonopioid analgesics.

Design: PANSAID is a randomized, blinded, placebo-controlled, four-group trial with 90 days follow-up.

Setting: Six Danish hospitals.

Participants: 556 patients with total hip arthroplasty from December 2015 to October 2017.

Intervention: Participants randomized to Group A paracetamol 1 g and ibuprofen 400 mg; Group B paracetamol 1 g and placebo; Group C ibuprofen 400 mg and placebo; or Group D paracetamol 0.5 g and ibuprofen 200 mg; orally, every six hours for 24 hours postoperatively, starting one hour before surgery.

Main outcomes: Two preplanned co-primary outcomes: 24-hours morphine consumption using patient-controlled analgesia in pairwise comparisons between the four groups; and proportion of patients with one or more serious adverse event (SAEs) within 90 days in groups A, C and D combined versus group B.

Results: 556 were analyzed (mean age, 67 years, 277 (50%) women). The median (interquartile range) 24-hour morphine consumption in group A, B, C, and D was 20 (12-40), 36 (24.5-52) mg, 26 (18-46), and 28 (18-46) respectively. The largest median difference was 16 mg (99.6%CI: 6.5 to 24, P<0.001) between group A and B. The difference was 8 mg (99.6%CI: -1 to 14, P=.0011) between group B and D and 6 mg (99.6%CI: -2 to 16, P=.0024) between group A and C. The differences between group A and D (8 mg (99.6%CI: -2 to 16, P=.0051)) and group B and C (10 mg (99.6%CI: -2 to 16, P=.0044)) were not statistically significant adjusted for multiple comparisons and two co-primary outcomes. There was no difference between groups C and D (2 mg (99.6%CI: -10 to 7, P=.81).

The proportion of patients with SAEs in groups A, C, and D was 15% (97.5% CI: 12 to 20) and 11% (97.5% CI: 6 to 18) in group B. The relative risk of SAE in the groups A, C, and D compared with group B was 1.44 (97.5% CI: 0.79 to 2.45, P=.18).

Conclusion and relevance: Group A compared with group B reduced morphine consumption more than the minimal important difference. Using ibuprofen the first postoperative day does not statistically significant increase the proportion of SAEs.

Trial registration: Clinicaltrials.gov identifier: NCT02571361

ABSTRACT No 3: Group 3 is the control group for the SAE outcome

PAracetamol and NSAID in combination for postoperative analgesia after primary hip arthroplasty: The randomised, blinded, parallel 4-group PANSAID clinical trial

Importance: Multimodal postoperative analgesia is widely used but lacks direct evidence.

Objective: Investigate beneficial and harmful effects of 4 nonopioid analgesics.

Design: PANSAID is a randomized, blinded, placebo-controlled, four-group trial with 90 days follow-up.

Setting: Six Danish hospitals.

Participants: 556 patients with total hip arthroplasty from December 2015 to October 2017.

Intervention: Participants randomized to Group A paracetamol 1 g and ibuprofen 400 mg; Group B paracetamol 1 g and placebo; Group C ibuprofen 400 mg and placebo; or Group D paracetamol 0.5 g and ibuprofen 200 mg; orally, every six hours for 24 hours postoperatively, starting one hour before surgery.

Main outcomes: Two preplanned co-primary outcomes: 24-hours morphine consumption using patient-controlled analgesia in pairwise comparisons between the four groups; and proportion of patients with one or more serious adverse event (SAEs) within 90 days in groups A, C and D combined versus group B.

Results: 556 were analyzed (mean age, 67 years, 277 (50%) women). The median (interquartile range) 24-hour morphine consumption in group A, B, C, and D was 20 (12-40), 36 (24.5-52) mg, 26 (18-46), and 28 (18-46) respectively. The largest median difference was 16 mg (99.6%CI: 6.5 to 24, P<0.001) between group A and B. The difference was 8 mg (99.6%CI: -1 to 14, P=.0011) between group B and D and 6 mg (99.6%CI: -2 to 16, P=.0024) between group A and C. The differences between group A and D (8 mg (99.6%CI: -2 to 16, P=.0051)) and group B and C (10 mg (99.6%CI: -2 to 16, P=.0044)) were not statistically significant adjusted for multiple comparisons and two co-primary outcomes. There was no difference between groups C and D (2 mg (99.6%CI: -10 to 7, P=.81).

The proportion of patients with SAEs in the groups 1, 2, and 4 was 14% (97.5% CI: 10 to 18) and 19% (97.5% CI: 13 to 28) in group 3. The relative risk of SAE in the groups 1, 2, and 4 compared with group 3 was 0.72 (97.5% CI: 0.45 to 1.17, P=.13).

Conclusion and relevance: Group 3 compared with group 4 reduced morphine consumption more than the minimal important difference. Using ibuprofen the first postoperative day does not statistically significant decrease the proportion of SAEs.

Trial registration: Clinicaltrials.gov identifier: NCT02571361

ABSTRACT No 4: Group 4 is the control group for the SAE outcome

PAracetamol and NSAID in combination for postoperative analgesia after primary hip arthroplasty: The randomised, blinded, parallel 4-group PANSAID clinical trial

Importance: Multimodal postoperative analgesia is widely used but lacks direct evidence.

Objective: Investigate beneficial and harmful effects of 4 nonopioid analgesics.

Design: PANSAID is a randomized, blinded, placebo-controlled, four-group trial with 90 days follow-up.

Setting: Six Danish hospitals.

Participants: 556 patients with total hip arthroplasty from December 2015 to October 2017.

Intervention: Participants randomized to Group A paracetamol 1 g and ibuprofen 400 mg; Group B paracetamol 1 g and placebo; Group C ibuprofen 400 mg and placebo; or Group D paracetamol 0.5 g and ibuprofen 200 mg; orally, every six hours for 24 hours postoperatively, starting one hour before surgery.

Main outcomes: Two preplanned co-primary outcomes: 24-hours morphine consumption using patient-controlled analgesia in pairwise comparisons between the four groups; and proportion of patients with one or more serious adverse event (SAEs) within 90 days in groups A, C and D combined versus group B.

Results: 556 were analyzed (mean age, 67 years, 277 (50%) women). The median (interquartile range) 24-hour morphine consumption in group A, B, C, and D was 20 (12-40), 36 (24.5-52) mg, 26 (18-46), and 28 (18-46) respectively. The largest median difference was 16 mg (99.6%CI: 6.5 to 24, P<0.001) between group A and B. The difference was 8 mg (99.6%CI: -1 to 14, P=.0011) between group B and D and 6 mg (99.6%CI: -2 to 16, P=.0024) between group A and C. The differences between group A and D (8 mg (99.6%CI: -2 to 16, P=.0051)) and group B and C (10 mg (99.6%CI: -2 to 16, P=.0044)) were not statistically significant adjusted for multiple comparisons and two co-primary outcomes. There was no difference between groups C and D (2 mg (99.6%CI: -10 to 7, P=.81).

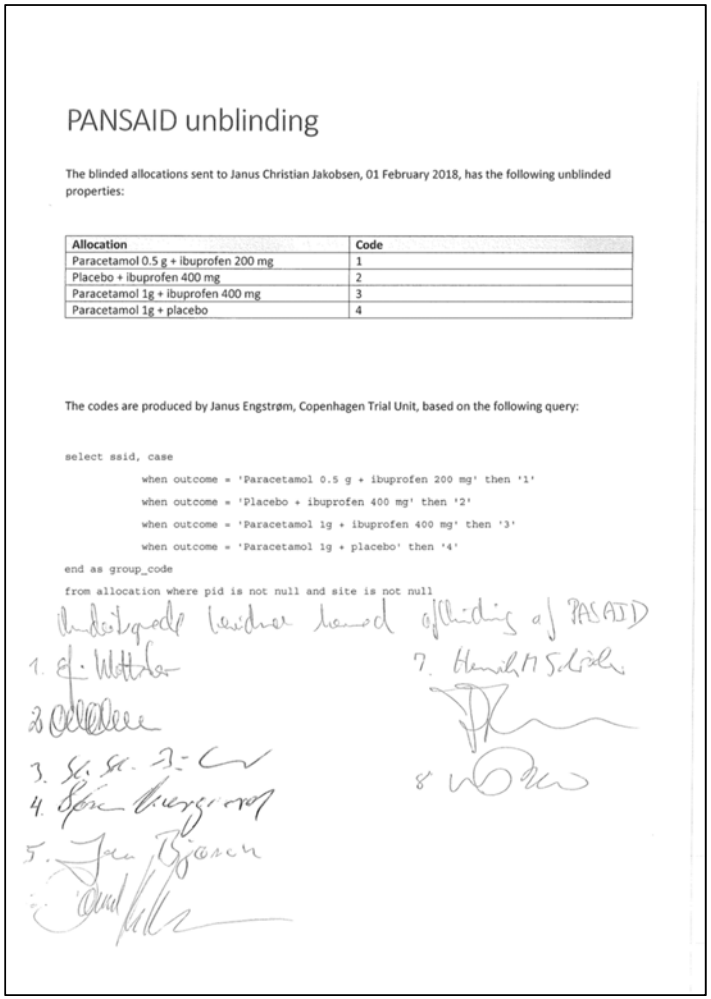
The proportion of patients with SAEs in groups 1, 2, and 3 was 17% (97.5% CI: 13 to 21) and 11% (97.5% CI: 6 to 18) in group 4. The relative risk of SAE in the groups 1, 2, and 3 compared with group 4 was 1.58 (97.5% CI: 0.87 to 2.88, P=.09).

Conclusion and relevance: Group 3 compared with group 4 reduced morphine consumption more than the minimal important difference. Using ibuprofen the first postoperative day does not statistically significant increase the proportion of SAEs.

Trial registration: Clinicaltrials.gov identifier: NCT02571361

eAppendix 3. Breaking the Blind

Unblinding with signatures



PANSAID unblinding

The blinded allocations sent to Janus Christian Jakobsen, 01 February 2018, has the following unblinded properties:

Allocation	Code
Paracetamol 0.5 g + ibuprofen 200 mg	1
Placebo + ibuprofen 400 mg	2
Paracetamol 1g + ibuprofen 400 mg	3
Paracetamol 1g + placebo	4

The codes are produced by Janus Engstrøm, Copenhagen Trial Unit, based on the following query:

```
select ssid, case
            when outcome = 'Paracetamol 0.5 g + ibuprofen 200 mg' then '1'
            when outcome = 'Placebo + ibuprofen 400 mg' then '2'
            when outcome = 'Paracetamol 1g + ibuprofen 400 mg' then '3'
            when outcome = 'Paracetamol 1g + placebo' then '4'
end as group_code
from allocation where pid is not null and site is not null
```

eAppendix 4. Preparing of the Trial Database

SOP: Cleaning the data-file

This SOP describes how the raw data file will be cleaned before it is send to the independent statistician.

Two independent investigators (Laura Kruuse and Kasper Thybo) will clean the data-file. Comparisons will be made for errors and a third person (Ole Mathiesen) will resolve disagreements. If consensus is not obtained, the PANSAID-steering committee will resolve the case.

The principle investigator will print a version of the raw data, sign, date, and archive it. The two independent investigators will print, sign, date, and archive their final version before comparison. The final version will be printed, signed, and archived as well. An anonymized version of the final file will be published as according to the PANSAID-protocol.

Detailed information on the adverse event and data regarding the follow-up period can be found in different data files.

The data file shall contain the following variables:

Variable	Description	Unit of measurement	Type of measurement	Definition
ID	Study ID nummer		Categorical	Equals “Study Subject ID”
CPR	Social security number			
Site	Site of inclusion		Categorical	Convert from “Protocol ID”: “PANSAID – NH” → NH “PANSAID – KH” → KH “PANSAID – NFH” → NFH “PANSAID – GH” → GH “PANSAID – OUH” → OUH “PANSAID – HH” → HH
Randomization_group			Categorical	
Age	The patients age	Years	Continuous	Years from date of birth to date of surgery
ASA	American Society of Anesthesiologists physical score		Ordinal	“1”, “2”, or “3”

Variable	Description	Unit of measurement	Type of measurement	Definition
Height		cm	Continuous	
Weight		kg	Continuous	
BMI	Body Mass Index	kg/m2	Continuous	
Sex			Binary	“Female”, “male”
Analgesics				
Paracetamol_prior	Prior use of paracetamol		Ordinal	“No use”, “daily use”, or “as needed”
ibuprofen_prior	Prior use of ibuprofen		Ordinal	“No use”, “daily use”, or “as needed”
Tramadol_prior	Prior use of tramadol		Ordinal	“No use”, “daily use”, or “as needed”
Codeine_prior	Prior use of codeine		Ordinal	“No use”, “daily use”, or “as needed”
NSAID_other_prior	Prior use of other NSAID		Ordinal	“No use”, “daily use”, or “as needed”
NSAID_prior	Prior use of NSAID		Ordinal	“No use”, “daily use”, or “as needed” This variable will merge the variables “ibuprofen” and “NSAID_other”
Surgery				
Surgery	Type of surgery		Categorical	KNFB20 → “uncemented” KNFB30 → “hybrid” KNFB40 → “cemented”
Surgery_time	Time from start of surgery to end of surgery	min	Continuous	
Anesthesia	Type of anesthesia		Categorical	“General anesthesia” “Spinal anesthesia” “Spinal anesthesia with sedation” “Conversion of spinal anesthesia to general anesthesia”
Sufentanil	Amount of sufentanil used at the end of surgery	ug	Continuous	Only relevant if “general anesthesia” or “conversion of spinal anesthesia to general anesthesia”
Bupivacaine	Amount of bupivacaine used for spinal anaesthesia	ml	Continuous	Only relevant if “spinal anesthesia”, “spinal anesthesia with sedation”, or “conversion of spinal anesthesia to general anesthesia”
Anesthesia_protocol	Did the anaesthesia follow the protocol described		Binary	“Yes” or “no”

Variable	Description	Unit of measurement	Type of measurement	Definition
Other_opioids_intra	Opioids other than sufentanil givin intraoperatively converted to morphine-equivalents (iv)	mg	Continuous	Conversion of opioids shall follow the table below.
Other_opioids_pre	Opioids given preoperatively		Binary	“Yes” or “no”
Bloodloss	Bloood loss intraoperatively	ml	Continuous	
Steroids_pre	Dexamethasone, methylprednisolone, or other steroids given pre- or peroperatively		Binary	“Yes” or “no”
Ondansetron_pre	Ondansetron given pre- or peroperatively		Binary	“Yes” or “no”
Local_anesthetic	Local anesthesia given intraarticular, as local infiltration, or as peripheral nerve block		Binary	“Yes” or “no”
intrathecal_opioids	Opioids given intrathecal		Binary	“Yes” or “no”
Intervention period – opioids				
PCA_morphine	The use of PCA-morphine from T0 to T24	mg	Continuous	
Morphine_1hour	The use of morphine the first hour postoperatively	mg	Continuous	
Opioid_intervention_period	The use of non-PCA opioids in the intervention period. Converted to morphine equivalents	mg	Continuous	

Variable	Description	Unit of measurement	Type of measurement	Definition
Morphine	The use of morphine from T0 to T24	mg	Continuous	This will be the sum of opioids given as addition boluses the first hour after surgery, the PCA-morphine, and other opioids (converted to morphine equivalents).
PCA	Use of PCA-morphine exclusively		Binary	“Yes” or “no”
Study_medication				
Tpre_surgery	Did the patient get this dosage		Binary	“Yes” or “or”
T6	Did the patient get this dosage		Binary	“Yes” or “or”
T12	Did the patient get this dosage		Binary	“Yes” or “or”
T18	Did the patient get this dosage		Binary	“Yes” or “or”
Other_analgesic_intervention_period	Did the patient get any non-opioid analgesic (not the study medication) in the intervention period		Binary	“Yes” or “no”
PAIN				See Note #1
VAS_rest_6h	Pain at rest at T6	mm	Continuous	All values from HH shall be multiplied by 10. Values that are “numeric rating scale” or from 0-10 shall also be multiplied by 10.
VAS_mob_6h	Pain during 30 degrees flexion of the hip at T6	mm	Continuous	All values from HH shall be multiplied by 10. Values that are “numeric rating scale” or from 0-10 shall also be multiplied by 10.
VAS_rest_24h	Pain at rest at T24	mm	Continuous	All values from HH shall be multiplied by 10. Values that are “numeric rating scale” or from 0-10 shall also be multiplied by 10.
VAS_mob_24h	Pain during 30 degrees flexion of the hip at T24	mm	Continuous	All values from HH shall be multiplied by 10. Values that are “numeric rating scale” or from 0-10 shall also be multiplied by 10.
Opioid related adverse effects				
Nausea_6h	Nausea at T6		Ordinal	“None”, “mild”, “moderate”, or “severe”

Variable	Description	Unit of measurement	Type of measurement	Definition
Nausea_24h	Nausea at T24		Ordinal	“None”, “mild”, “moderate”, or “severe”
Sedation_6h	Sedation at T6		Ordinal	“None”, “mild”, “moderate”, or “severe”
Sedation_24h	Sedation at T24		Ordinal	“None”, “mild”, “moderate”, or “severe”
Dizziness_6h	Dizziness at T6		Ordinal	“None”, “mild”, “moderate”, or “severe”
Dizziness_24h	Dizziness at T24		Ordinal	“None”, “mild”, “moderate”, or “severe”
Vomiting_0_6h	Vomiting from T0 to T6		COUNT	Number of vomiting episodes
Vomiting_6_24h	Vomiting from T6 to T24		COUNT	Number of vomiting episodes
Ondansetron	Consumption of ondansetron from T0 to T24	mg	Continuous	
Dexamethasone	Use of dexamethasone in the intervention period		Binary	“Yes” or “no”
DHB	Use of DHB in the intervention period		Binary	“Yes” or “no”
**Adverse events				See Note #2
AE	Did this patient have one or more AE		Binary	“Yes” or “no”
SAE	Did this patient have one or more SAE. Excluding SAE resulting from prolongation of hospitalisation		Binary	“Yes” or “no”
Populations				
mITT	Will this patient be included in the mITT population		Binary	“Yes” or “no”
sPP	Will this patient be included in the sPP population		Binary	“Yes” or “no”
sPP_safety_variables	Will this patient be included in the sPP		Binary	“Yes” or “no”

Variable	Description	Unit of measurement	Type of measurement	Definition
	for safety variables population			

Note #1: All pain scores from Holbæk Hospital used the Numeric rating scale (scale 0-10) and not the Visual analog scale (0-100), and therefore all pain scores shall be multiplied by 10.

Note #2: According to the PANSAID protocol, SAEs are not considered an SAE if only the criterion of "prolongation of hospitalization" is fulfilled.

Definition of populations:

The Primary analysis population: modified intention to treat (mITT) population:

All patients randomized AND having THA surgery will be included in the mITT

The strictly per protocol (sPP) population:

The sPP population will consist of patients from the mITT population excluding the following patients:

- Patients with a major protocol violation
- Patients given non-opioid analgesics other than the study medication in intervention period (T0 to T24). E.g. paracetamol, NSAIDs, intrathecal opioids, steroids, local infiltration analgesia, etc.

Chlorzoxazone will not be considered an analgesic medication.

Major protocol violations are defined as:

1. Patients that did not get any of the dosages of the randomized allocated trial treatment, or

2. Patients withdrawing from the trial intervention allowing the use of registered data, or

3. Patients undergoing additional surgery (besides the elective THA) or a procedure in the intervention period that requires anaesthesia or sedation and/or analgesia.

The strictly per protocol (sPP) population for safety variables:

The sPP analyses regarding SAEs and other safety variables will include patients with major protocol violation definition number 3.

The populations have been defined in the protocol [1] and the detailed statistical analysis plan [2].

Conversion of opioids:

Conversion of opioids will follow the table below. All opioids are converted to intravenous morphine equivalents.

If oxycodone or morphine are given pre- or peri-operatively it will be converted to morphine equivalents and added to the 24 hour morphine consumption (like opioids given in the intervention period).

Appendix 2: Opioid conversion table used to equate equivalent i.v. morphine values.

1mg morphine oral	0.33 mg morphine i.v. *
1mg fentanyl i.v.	100 mg morphine i.v.*
1mg oxycodone i.v.	1.33 mg morphine i.v. *
1mg oxycodone oral	0.5 mg morphine i.v. *
1mg tramadol oral	0.07 mg morphine i.v. *
1mg ketobemidone i.v.	1 mg morphine i.v. *
1mg ketobemidone oral	0.67 mg morphine i.v. *
1mg sufentanil i.v.	1000 mg morphine i.v. *
1mg hydromorphone i.v.	6.67 mg morphine i.v. **
1mg meperidine i.v.	0.13 mg morphine i.v. **

* Akut smerte (Acute pain) application, Ph.D. Ole Mathiesen, Rigshospitalet Copenhagen

** http://www.globalrph.com/narcotic.cgi

SOP Clean file Follow-up data

This SOP be describe the data file containing the clean file for the follow-up period.

Two independent investigators (Laura Kruuse and Kasper Thybo) will clean the data-file (from OpenClinica). Comparisons will be made for errors and a third person (Ole Mathiesen) will resolve disagreements. If consensus is not obtained, the PANSAID-steering committee will resolve the case.

The principal investigator will print a version of the raw data, sign, date, and archive it. The two independent investigators will print, sign, date, and archive their final version before comparison. The final version will be printed, signed, and archived as well. An anonymized version of the final file will be published as according to the PANSAID-protocol.

Variable	Description	Unit of measurement	Type of measurement	Definition
ID	Study ID number		Categorical	Study subject ID
CPR	Ssocial security number			
Paracetamol_follow_up	Did the patient receive NSAID in the follow-up period. Number of days. From SP2a		Categorical	“No”, “0_3”, “4_7”, “8_30”, “31_90”.
NSAID_follow_up	Did the patient receive NSAID in the follow-up period. Number of days. From SP3a and SP4a		Categorical	“No”, “0_3”, “4_7”, “8_30”, “31_90”.
Medical_attention	Self-reported need for medical attention		Categorical	“No”, “GP”, “hospital”, “both”
SAE_questionnaire	Did this patient have one or more SAE in the follow-up period. According to the questionnaire		Binary	“Yes” or “no”
SAE_LPR	Did this patient have one or more SAE in the follow-up period. Hospitalization and death. From the Danish National Patient Registry and the Civil Registration System.		Binary	“Yes” or “no”
SAE_follow_up	Combined			
Days_alive_outside_hospital	Number of days from the surgery (T0) to 90 days postoperatively spend alive and outside hospital. From the National Patient Registry.	days	Count	

Note: the co-primary outcome of SAE will merge the SAEs in the intervention period and the SAEs in the follow-up period.

eTable 1. Interaction Between Site and Intervention for Pairwise Comparisons of Primary and Secondary Outcomes

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Morphine consumption				
Group PCM+IBU	-	0.01	0.21	0.003[#]
Group PCM	-	-	0.32	0.94
Group IBU	-	-	-	0.10
Pain, rest, 6h				
Group PCM+IBU	-	0.08	0.36	0.01
Group PCM	-	-	0.51	0.98
Group IBU	-	-	-	0.18
Pain, mobilization, 6h				
Group PCM+IBU	-	0.44	0.31	0.51
Group PCM	-	-	0.43	0.73
Group IBU	-	-	-	0.55
Pain, rest, 24h				
Group PCM+IBU	-	0.10	0.72	0.79
Group PCM	-	-	0.02	0.17
Group IBU	-	-	-	0.31

The numbers reported in the table are P-values for interaction between site and intervention. [#] indicates statistically significant results according to the level of significance for primary (0.0042) and secondary outcomes (0.0084)

eTable 1, continued

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Pain, mobilization, 24h				
Group PCM+IBU	-	0.06	0.0002[#]	0.05
Group PCM	-	-	0.07	0.39
Group IBU	-	-	-	0.14
AE				
Group PCM+IBU		0.78	0.62	0.62
Group PCM	-	-	0.80	0.60
Group IBU	-	-	-	0.95

The numbers reported in the table are P-values for interaction between site and intervention. [#] indicates statistically significant results according to the level of significance for primary (0.0042) and secondary outcomes (0.0084)

eTable 2. Interaction Between Site and Intervention for the Primary Outcomes of Patients With 1 or More Modified SAEs

Comparison	p-value for interaction between site and intervention
Group PCM+IBU, IBU, and HS-PCM+IBU vs Group PCM	N/A

N/A, not available because of perfect prediction and collinearity.

eTable 3. Patients Taking NSAID in the Follow-up Period

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
No use, n (%)	37 (27)	25 (18)	35 (25)	32 (23)
Any use, n (%)	93 (68)	114 (80)	98 (71)	104 (75)
Missing data, n (%)	6 (5)	3 (2)	6 (4)	3 (2)
Total, n	136	142	139	139

Chi-sq: P=0.21

eTable 4. Types of SAEs

	Group PCM+IBU	Group PCM	Group IBU	Group PCM500+ IBU200
Related to surgery				
Surgical site infection, n	5	4	5	4
Mechanical problems with the prosthesis, n	5	4	3	1
Sub total, n	*10*	*8*	*8*	*5*
Medical problems after surgery				
Pneumonia, n	1		2	
DVT, n	1		2	
PE, n	1	1		
low hemoglobin, n	2			1
Delirium, n				1
Syncope, n				1
Vertigo, n				2
Cardiological, n	1	1	3	3
Dyspepsia, n	1			
Renal, n	1			
Constipated, n	1			
Abdominal pain, n				2
Sub total, n	*9*	*2*	*7*	*10*
"Not" related to the surgery				
Infection: not anatomical related, n	1	1	1	1
Fracture, not anatomical related, n			1	
Unknown, n	5	4	3	2
Sub total, n	*7*	*5*	*5*	*3*
Total, n	26	15	20	18

DVT= deep venous thrombosis; PE=pulmonary embolism;

In group IBU: one patient with pneumonia also had a cardiological complication, one patient with pneumonia also had constipation. Post hoc analyses of medical problems comparing ibuprofen vs paracetamol: Relative risk: 4.46 (95% CI 1.07 to 18.5), P=0.02

eTable 5. Types of Adverse Events

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Hematuria, n	1			
Bradycardia, n				1
Confusion, n	2	3	4	1
Dyspepsia, n	3	4	1	5
Elevated creatinine, n			1	1
Fall, n	1			
Fever, n		1	1	
Headache, n			1	
Hot flush when using PCA-morphine, n			2	1
Itching, PCA, n	7	5	3	2
Incontinence (stool), n				1
Leaking from surgical site, n		1	1	
Low blood pressure, n			3	
Low hemoglobin, n	3		2	2
Low potassium, n				1
Nausea, n		1		1
Not mobilized, n		1		1
Pain when using PCA-morphine, n				1
Ructus, n				1
Shivering, n		1		
Sleep disorder, n	1	2	1	
Syncope during mobilization, n	1			
Transfer to another hospital, n			1	
Dry mouth, n		1		1
Vasovagal episode during anesthesia, n				1
Vasovagal episode during mobilization, n	1	3	1	
Total, n	20	23	22	21

eTable 6. Exploratory Outcomes

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Nausea, 6 hours, %	**16**	**23**	**15**	**21**
Group PCM+IBU*	-	0.71 (0.43 to 1.15) P=.17	1.07 (0.61 to 1.86) P=.82	0.78 (0.47 to 1.29) P=.33
Group PCM*	-	-	1.51 (0.91 to 2.50) P=.11	1.10 (0.70 to 1.72) P=.67
Group IBU*	-	-	-	0.73 (0.43 to 1.23) P=.24
Nausea, 24 hours, %	**13**	**24**	**23**	**28**
Group PCM+IBU*	-	0.53 (.31 to 0.90) P=.019#	0.56 (0.32 to 0.96) P=.036#	0.45 (0.27 to 0.76) P=.003#
Group PCM*	-	-	1.06 (0.69 to 1.63) P=.79	0.86 (0.57 to 1.28) P=.45
Group IBU*	-	-	-	0.81 (0.53 to 1.22) P=.31
Sedation, 6 hours, %	**24**	**37**	**21**	**29**
Group PCM+IBU*	-	0.66 (0.46 to 0.96) P=.028#	1.18 (0.75 to 1.84) P=.48	0.85 (0.57 to 1.27) P=.42
Group PCM*	-	-	1.78 (1.19 to 2.66) P=.005#	1.28 (0.91 to 1.81) P=.16
Group IBU*	-	-	-	0.72 (0.47 to 1.11) P=.14
Sedation, 24 hours, %	**33**	**42**	**36**	**42**
Group PCM+IBU*	-	0.78 (0.57 to 1.06) P=.11	0.92 (0.66 to 1.29) P=.63	0.78 (0.57 to 1.06) P=.12
Group PCM*	-	-	1.19 (0.88 to 1.61) P=.26	1.00 (0.76 to 1.32) P=.99
Group IBU*	-	-	-	0.84 (0.62 to 1.14) P=.27
Dizziness, 6 hours, %	**14**	**25**	**20**	**24**
Group PCM+IBU*	-	0.56 (0.34 to 0.93) P=.024#	0.70 (0.41 to 1.21) P=.20	0.58 (0.35 to 0.98) P=.041#
Group PCM*	-	-	1.26 (0.80 to 1.97) P=.31	1.05 (0.69 to 1.59) P=.83
Group IBU*	-	-	-	0.83 (0.53 to 1.31) P=.43

All differences are 'left column compared with (minus) top row'. Level of significance 0.05. # indicates statistically significant p value. * Relative Risk (95% confidence interval). ** Median difference (95% confidence interval)

eTable 6, continued

	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

All differences are 'left column compared with (minus) top row'. Level of significance 0.05. # indicates statistically significant p value. * Relative Risk (95% confidence interval). ** Median difference (95% confidence interval)

eTable 7. Strictly Per Protocol Population

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Primary analysis population, n	136	142	139	139
Strictly Per Protocol population, n	120	130	126	128
Reasons for exclusion from the Primary analysis				
Protocol violation No 1, n	0	0	2	0
Protocol violation No 2, n	4	9	6	7
Protocol violation No 3, n	2	0	0	0
Use of other analgesics in the intervention period	10	3	4	3
Transfer to another hospital, n	0	0	1	1
Subtotal, n	16	12	13	11

eTable 8. Withdrawn Because of Opioid-associated Adverse Effects or Insufficient Pain Treatment

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Primary analysis population, n	136	142	139	139
Withdrawn because of opioid-associated adverse effects or insufficient pain treatment, n	2	5	3	3

Fischers exact test: P=.8

eTable 9. Analyses Adjusted for Age, Sex, Prior Use of Paracetamol, and Prior Use of NSAID for the Co-Primary Outcome of Morphine Consumption with 95% CIs

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Morphine consumption				
Group PCM+IBU	-	-13 (-19 to -8), P<.001	-5 (-10 to 0), P=.05	-5 (-10 to 0), P=.06
Group PCM	-	-	9 (4 to 14), P=.001	8 (3 to 14), P=.002
Group IBU	-	-	-	0 (-5 to 5), P=.94

The reported numbers are mean differences (95% CI) using GEE. Differences are 'left column compared with (minus) top row'. Adjusted for age, sex, prior use of paracetamol, and prior use of NSAID. CI, confidence interval.

eTable 10. Analyses on the Strictly Per Protocol Population for the Co-Primary Outcome of Morphine Consumption

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Morphine consumption				
Group PCM+IBU	-	-15 (-21 to -9), P<.001	-7 (-12 to -1), P=.02	-6 (-12 to -1), P=.03
Group PCM	-	-	8 (3 to 14), P=.004	9 (3 to 15), P=.004
Group IBU	-	-	-	0 (-5 to 6), P=.91

The reported numbers are mean differences (95% CI) using GEE. Differences are 'left column compared with (minus) top row'. CI, confidence interval.

eTable 11. Adjusted Analyses of Secondary Outcomes

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Difference in pain during mobilization at 6 hours				
Group PCM+IBU	-	-7 (-13 to -1) P=.02	-4 (-10 to 2) P=.16	-7 (-13 to -1) P=.01
Group PCM	-	-	3 (-3 to 9) P=.32	0 (-6 to 6) P=.98
Group IBU	-	-	-	-3 (-9 to 2) P=.26
Difference in pain at rest at 6 hours				
Group PCM+IBU	-	-8 (-13 to -2) P=.005	-5 (-10 to 0) P=.05	-4 (-9 to 1) P=.10
Group PCM	-	-	3 (-3 to 8) P=.35	3 (-2 to 9) P=.19
Group IBU	-	-	-	1 (-4 to 6) P=.70
Difference in pain during mobilization at 24 hours				
Group PCM+IBU	-	-11 (-17 to -6) P<.001	-8 (-13 to -2) P=.008	-8 (-14 to -2) P=.005
Group PCM	-	-	4 (-2 to 10) P=.21	4 (-2 to 10) P=.19
Group IBU	-	-	-	0 (-6 to 6) P=.91
Difference in pain at rest at 24 hours				
Group PCM+IBU	-	-11 (-15 to -6) P<.001	-7 (-12 to -3) P<.001	-5 (-9 to -2) P=.007
Group PCM	-	-	3 (-2 to 8) P=.19	6 (1 to 10) P=.01
Group IBU	-	-	-	2 (-2 to 7) P=.28
RR, Adverse events				
Group PCM+IBU	-	0.96 (0.56 to 1.65) P=.88	0.95 (0.55 to 1.65) P=.86	1.02 (0.58 to 1.78) P=.94
Group PCM	-	-	1.02 (0.60 to 1.74) P=.94	1.09 (0.63 to 1.90) P=.75
Group IBU	-	-	-	1.08 (0.62 to 1.88) P=.79

Differences are 'left column compared with (minus) top row'. Adjusted for age, sex, prior use of paracetamol, and prior use of NSAID. Data are mean differences in mm (99.2% CI) or RR= relative risk (99.2% CI). Mobilization = 30 degree flexion of the hip

eTable 12. Analyses on the Strictly Per Protocol Population of Secondary Outcomes

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Difference in pain during mobilization at 6 hours				
Group PCM+IBU	-	-7 (-13 to -0) P=.05	-4 (-10 to 3) P=.25	-7 (-13 to -1) P=.02
Group PCM	-	-	3 (-3 to 9) P=.35	-1 (-7 to 5) P=.85
Group IBU	-	-	-	-4 (-9 to 2) P=.22
Difference in pain at rest at 6 hours				
Group PCM+IBU	-	-8 (-13 to -2) P=.007	-5 (-10 to 1) P=.09	-4 (-9 to 1) P=.11
Group PCM	-	-	3 (-3 to 8) P=.32	3 (-2 to 9) P=.22
Group IBU	-	-	-	1 (-5 to 6) P=.83
Difference in pain during mobilization at 24 hours				
Group PCM+IBU	-	-12 (-18 to -6) P<.001	-9 (-15 to -3) P=.003	-9 (-15 to -3) P=.004
Group PCM	-	-	3 (-3 to 9) P=.32	3 (-3 to 9) P=.31
Group IBU	-	-	-	0 (-6 to 6) P=.99
Difference in pain at rest at 24 hours				
Group PCM+IBU	-	-12 (-17 to -8) P<.001	-8 (-13 to -4) P<.001	-7 (-11 to -3) P=.001
Group PCM	-	-	4 (-1 to 9) P=.13	5 (1 to 10) P=.03
Group IBU	-	-	-	2 (-3 to 6) P=.49
RR, Adverse events				
Group PCM+IBU	-	1.29 (0.69 to 2.38) P=.42	1.11 (0.61 to 2.01) P=.73	1.13 (0.62 to 2.04) P=.70
Group PCM	-	-	0.86 (0.46 to 1.61) P=.64	0.88 (0.47 to 1.64) P=.68
Group IBU	-	-	-	1.02 (0.55 to 1.86) P=.96

Differences are 'left column compared with (minus) top row'. Data are mean in mm (99.2% CI) or RR= relative risk (99.2% CI). Mobilization = 30 degree flexion of the hip

eTable 13. Analyses on the Strictly Per Protocol Population of Exploratory Outcomes

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Nausea, 6 hours, %				
Group PCM+IBU*	-	0.70 (0.43 to 1.17) P=.17	1.21 (0.67 to 2.19) P=.54	0.91 (0.53 to 1.56) P=.72
Group PCM*	-	-	1.71, (1.00 to 2.93) P=.05	1.29 (0.80 to 2.08) P=.31
Group IBU*	-	-	-	0.75 (0.42 to 1.33) P=.33
Nausea, 24 hours, %				
Group PCM+IBU*	-	0.51 (0.29 to 0.90) P=.02	0.55 (0.31 to 0.97) P=.04	0.45 (0.26 to 0.78) P=.004
Group PCM*	-	-	1.07 (0.69 to 1.66) P=.76	0.88 (0.58 to 1.32) P=.52
Group IBU*	-	-	-	0.82 (0.54 to 1.25) P=.35
Sedation, 6 hours, %				
Group PCM+IBU*	-	0.72 (0.49 to 1.04) P=.08	1.32 (0.83 to 2.12) P=.24	0.92 (0.61 to 1.38) P=.68
Group PCM*	-	-	1.85, (1.21 to 2.83) P=.004	1.28 (0.89 to 1.84) P=.18
Group IBU*	-	-	-	0.69 (0.44 to 1.09) P=.11
Sedation, 24 hours, %				
Group PCM+IBU*	-	0.79 (0.57 to 1.10) P=.16	0.94 (0.66 to 1.33) P=.72	0.76 (0.55 to 1.06) P=.10
Group PCM*	-	-	1.19 (0.87 to 1.63) P=.28	0.97 (0.73 to 1.29) P=.82
Group IBU*	-	-	-	0.81 (0.60 to 1.11) P=.19
Dizziness, 6 hours, %				
Group PCM+IBU*	-	0.56 (0.33 to 0.96) P=.03	0.76 (0.43 to 1.34) P=.34	0.63 (0.37 to 1.09) P=.10
Group PCM*	-	-	1.35 (0.84 to 2.16) P=.22	1.12 (0.72 to 1.74) P=.60
Group IBU*	-	-	-	0.83 (0.51 to 1.37) P=.47

Differences are 'left column compared with (minus) top row'. * Relative Risk (95% confidence interval). ** p-value (Van Elteren test) only.

eTable 13, continued

	Group PCM+IBU	Group PCM	Group IBU	Group HS-PCM+IBU
Dizziness, 24 hours %				
Group PCM+IBU*	-	0.82 (0.49 to 1.36) P=.44	0.60 (0.37 to 0.96) P=.04	0.63 (0.39 to 1.01) P=.06
Group PCM*	-	-	0.73 (0.48 to 1.12) P=.15	0.77 (0.50 to 1.18) P=.22
Group IBU*	-	-	-	1.04 (0.71 to 1.54) P=.83
Vomiting, 0-24 hours, number, median				
Group PCM+IBU**	-	P=.80	P=.90	P=.26
Group PCM**	-	-	P=.61	P=.37
Group IBU**	-	-	-	P=.18
Ondansetron, mg**				
Group PCM+IBU**	-	P=.18	P=.79	P=.13
Group PCM**	-	-	P=.11	P=.94
Group IBU**	-	-	-	P=.08
Blood loss, ml				
Group PCM+IBU**	-	P=.47	P=.39	P=.52
Group PCM**	-	-	P=.07	P=.19
Group IBU**	-	-	-	P=.88
Days alive and outside hospital, days				
Group PCM+IBU**	-	P=.74	P=.27	P=.80
Group PCM**	-	-	P=.70	P=.94
Group IBU**	-	-	-	P=.50

Differences are 'left column compared with (minus) top row'. * Relative Risk (95% confidence interval). ** p-value (Van Elteren test) only.