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FINAL STUDY REPORT

Full title of the trial:	A randomised, Double-blind, placEbo-controlled Study to assess the effectIveness of pectoral nerves block (Pecs) after breast surGery on Piritramide coNsumption.
Short title of the trial:	DESIGN
EudraCT Number	2015-005574-38
Sponsor Protocol Number:	IJB-SUR-DESIGN-2015
ClinicalTrials.gov Number:	NCT02655965
Sponsor:	Institut Jules Bordet Rue Meylemeersch,90 – 1070 Anderlecht Belgique/België
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Report date	11/01/2022

CONFIDENTIAL

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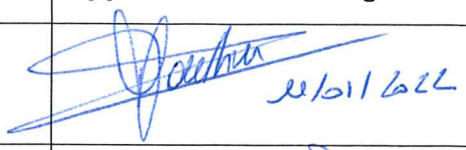
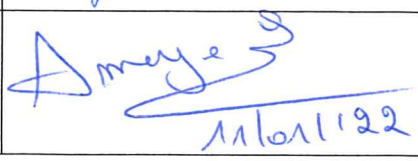
Marie-Pierre Gauthier	Pharmacovigilance Manager	
Lieveke Ameye	Statistician	

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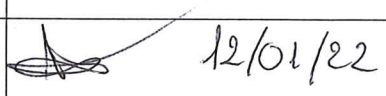
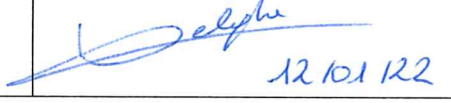
Nicolas Moretti	Data Manager	
Chloé Velghe	Project Manager	

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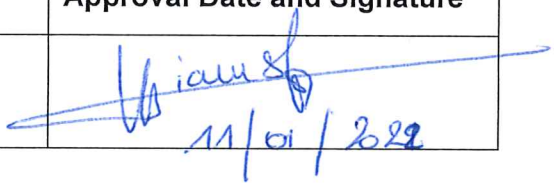
Dr Kathleen Wiams	MD, Study Chair	

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TRIAL INFORMATION

PHASE	Phase III
STUDY DESIGN	This is a double-blind study that will randomise in 1:1 ratio breast cancer subjects with a planned surgery to receive a “pecs block” of 10 ml of ropivacaine 3.5 mg/ml and clonidine 5 µg/ml injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior (arm A) versus 10 ml of placebo (sodium chloride 0.9 %) injected between pectoral muscles and 20 ml of the same solution between the muscles pectoralis minor and serratus anterior (arm B). The pecs block will be injected just before the surgery. Subjects will receive a nausea and vomiting prophylaxis depending on Apfel score. After surgery and if they present no contraindications, the two intervention groups will receive a dose of paracetamol (1 g) and diclofenac (75 mg) just before waking up, and a dose of 0.05 mg/kg piritramide. In the Post Anaesthesia Care Unit (PACU), the two groups will benefit from a Patient Controlled Intravenous Analgesia (PCIA) pump of piritramide allowing them to control their analgesia, which will be stopped 24 hours postoperatively.
STUDY RATIONALE	Despite the development of various treatments such as chemotherapy, radiotherapy and hormone therapy in breast cancer, complete tumour resection remains the treatment offering the best prognosis. However, it is frequently associated with the presence of postoperative pain and the development of chronic pain in the long term. In addition, surgery causes a stress response with cytokine production and various neuroendocrine mediators causing a decrease in immune function perioperatively. For several years, both the per- and postoperative analgesia is achieved through the use of opiates. But the use thereof remains associated with numerous side effects such as nausea, vomiting, respiratory depression, ileus and pruritus. Moreover, recent studies suggest an association between the use of these opiates and development of postoperative hyperalgesia. Other studies have also shown that opiates alter the humoral and cellular immune functions which may play a role in the recurrence of certain cancers[1]. Recently, the focus is on the use of loco-regional analgesia, which reduces surgical stress by blocking afferent neuronal transmission and preventing the harmful impulses from reaching the central nervous system. In a retrospective study of subjects undergoing surgery for breast cancer, Exadaktylos et al. showed that the combination of a paravertebral block with general anaesthesia was associated with a longer disease-free survival and

	a lower incidence of cancer recurrence[2]. More recently, a study on the combined use of paravertebral block and propofol in subjects with breast cancer, showed a decrease of pro-tumour cytokines, IL-1 and IL-8 and increased an antitumour cytokine, IL-10[3].However paravertebral block can be associated with many complications such as pneumothorax, spinal anaesthesia and intravascular injection[4]. R. Blanco et al recently described the "Pecs modified block" or type II block Pecs. This technique of ultrasound-guided anaesthesia locoregional aims to block the pectoral nerve, intercostobrachial, intercostal III-IV-V-VI and the long thoracic nerve, necessary for complete analgesia during breast surgery[5]. In a randomised study comparing the efficacy of analgesia pectoral nerve block compared to the paravertebral block among subjects receiving radical mastectomy, Wahba et al have demonstrated that block pecs reduced morphine consumption at 24 hours compared to the paravertebral block[6]. Therefore, the aims of this study are to compare the effectiveness of pecs block associated to a general anaesthesia in terms of piritramide consumption with the one of general anaesthesia alone and the chronic pain incidence.
OBJECTIVES	• Primary objective: To compare the effectiveness of pecs block associated to a general anaesthesia in terms of total piritramide consumption. • Secondary objectives : 1) To evaluate the incidence of chronic pain in both groups at 6 months postoperatively. 2) To evaluate in both groups the present pain intensity from wake-up until 48h postoperatively.
ENDPOINTS	• Primary endpoint: Total piritramide consumption during the first 24 h post-surgery. • Secondary endpoints: 1) Chronic pain intensity at 6 months postsurgery assessed by Mc Gill Pain Questionnaire 2) Present pain intensity until 48 hrs postsurgery assessed by Visual Analog scoring
INCLUSION CRITERIA	Subjects will only be eligible for study participation if they meet all the following inclusion criteria: 1. Age ≥18 years old 2. Female 3. Subjects undergoing either a conservative or non-conservative breast surgery associated with axillary dissection. 4. ASA score ≤ 3 5. Completion of all necessary screening procedures within 30 days prior to randomisation

	6. Adequate renal function including: Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 60 ml/min as calculated using the method standard for the institution 7. Adequate Liver Function, including all of the following parameters: a. Aspartate and Alanine Aminotransferase (AST and ALT) ≤ 1.5 x ULN. If Aspartate and Alanine aminotransferase (AST and ALT) are > 1.5 x ULN, total serum bilirubin should be assessed and must be ≤ 1.5 x ULN unless the patient has documented Gilbert Syndrome b. Alkaline phosphatase ≤ 2.5 x ULN 8. Signed informed consent 9. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures
EXCLUSION CRITERIA	Subjects who exhibit any of the following conditions at screening will not be eligible for admission into the study. 1. Any illness or medical condition that is unstable or could jeopardize the safety of the subject or her compliance with study requirements 2. Allergy to local anaesthetics 3. Known allergy or hypersensitivity to paracetamol, diclofenac, piritramide or excipients 4. Coagulopathy or taking oral anticoagulant/ antiaggregant within 7 days prior to surgery 5. BMI> 35 kg / m^2 6. Infection near the puncture site 7. Inability to understand the pain assessment scales (VAS and McGill questionnaire) 8. Severe hepatic impairment: elevated transaminases (AST/ALT > 5 x ULN) with factor V ≤ 50% 9. Severe heart failure: NYHA classification III or IV or LVEF < 50% 10. Pregnant or lactating women 11. Concurrent treatment with daily basis chronic opiate type painkillers not ended 1 month prior surgery 12. Scheduled breast reconstruction at the time of surgery 13. Metastatic subjects 14. Subjects with breast implants 15. Subjects that require bilateral mastectomy or bilateral lumpectomy
INVESTIGATIONAL MEDICINAL PRODUCTS	Arm A: ropivacaine 3.5 mg/ml and clonidine 5 µg/ml (10 ml injected between pectoral muscles and 20 ml

	between the muscles pectoralis minor and serratus anterior) Arm B: Placebo (sodium chloride 0.9% (NaCl 0.9%)) (10 ml injected between pectoral muscles and 20 ml between the muscles pectoralis minor and serratus anterior)
INDICATION	Locoregional analgesia in breast surgery
TARGET STUDY POPULATION	Breast cancer subjects undergoing either conservative or non-conservative breast surgery associated with axillary dissection
PARTICIPATING COUNTRY	Belgium
PARTICIPATING SITES NUMBER	1
LENGTH OF THE STUDY	3 years
INDEPENDENT DATA MONITORING COMMITTEE	N.A.
DATE OF GLOBAL END OF TRIAL	20 January 2021

1 SUBJECT INFORMATION

1.1 General information

57 subjects were registered and randomised in the DESIGN trial:

- 28 were randomised in the intervention arm: ropivacaine 3.5 mg/ml + clonidine 5 µg/ml
- 29 were randomised in the control arm (NaCl 0.9%)

The actual number of subjects registered in each age range for the whole trial is specified in the table 1.

Table 1: Age range for the whole trial

Age categorical characteristic	Intervention arm Number of subjects	Contol arm Number of subjects	Total
Between 18 and 65 years	22	23	45
From 66 years to 84 years	6	6	12
85 years and over	0	0	0
TOTAL	28	29	57

The median of subjects' age is 52 years (full range 30 - 83).

1.2 Subject disposition

57 subjects were registered in the trial and 55 were exposed to the investigational medicinal products (IMPs)

55 subjects completed the trial and 2 subjects did not complete the trial.

The reasons why some subjects did not complete the trial with the corresponding subjects' number are specified in the table 2.

Table 2: Non-completion reasons with corresponding subjects' number.

Non-completion reasons	**Number of subjects**
Subject's consent withdrawal	2

2 STATISTICAL ANALYSIS

The 55 subjects randomised in this trial were eligible for the statistical analysis.

2.1 Baseline characteristics (N = 55)

	Control arm (N = 28)		Intervention arm (N = 27)	
Age at surgery				
Mean ± std	52 ± 13		52 ± 13	
Median (Q1-Q3)	51 (32 to 83)		48 (30 to 79)	
Tumour laterality				
Left	15	54%	15	56%
Right	13	46%	12	44%
Clinical size of tumour: largest diameter (mm)				
Mean ± std	38 ± 31		30 ± 24	
Median (Q1-Q3)	30 (9 to 150)		25 (6 to 96)	
Histology				
Ductal	18	64%	20	74%
Lobular	6	21%	6	22%
Ductal and lobular	2	7%	-	-
Other	2	7%	1	4%
Concomitant disease*				
Cardiovascular disorders	5	18%	7	26%
Endocrine & metabolic disorders	7	25%	9	33%
Nervous system disorders	4	14%	6	22%
Gastrointestinal disorders	3	11%	5	19%
Injury/pain	11	39%	8	30%
Infections	3	11%	1	4%
Opthalmic disorder	0	0%	1	4%
Osteoarticular disorder	1	4%	0	0%
Previous surgery	11	39%	15	56%

	Control arm (N = 28)		Intervention arm (N = 27)	
Respiratory disorder	2	7%	1	4%

* Multiple answers possible

2.2 Breast cancer surgery (N=55)

	Control arm (N = 28)		Intervention arm (N = 27)	
Partial mastectomy	2	7%	-	-
Breast lumpectomy	8	29%	13	48%
Modified radical mastectomy	18	64%	14	52%
Radical mastectomy	-	-	-	-
Simple mastectomy	-	-	-	-
Other	-	-	-	-

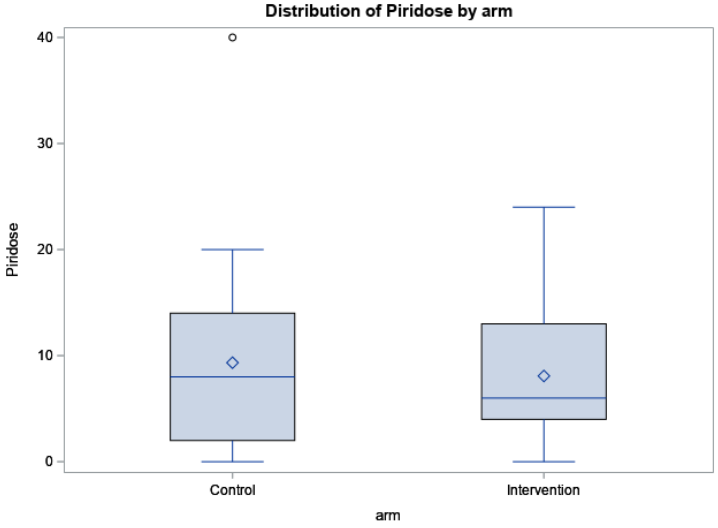
2.3 Piritramide consumption at 24 hours post-operatively

The perioperative piritramide consumption is available in 51 of the 55 subjects.

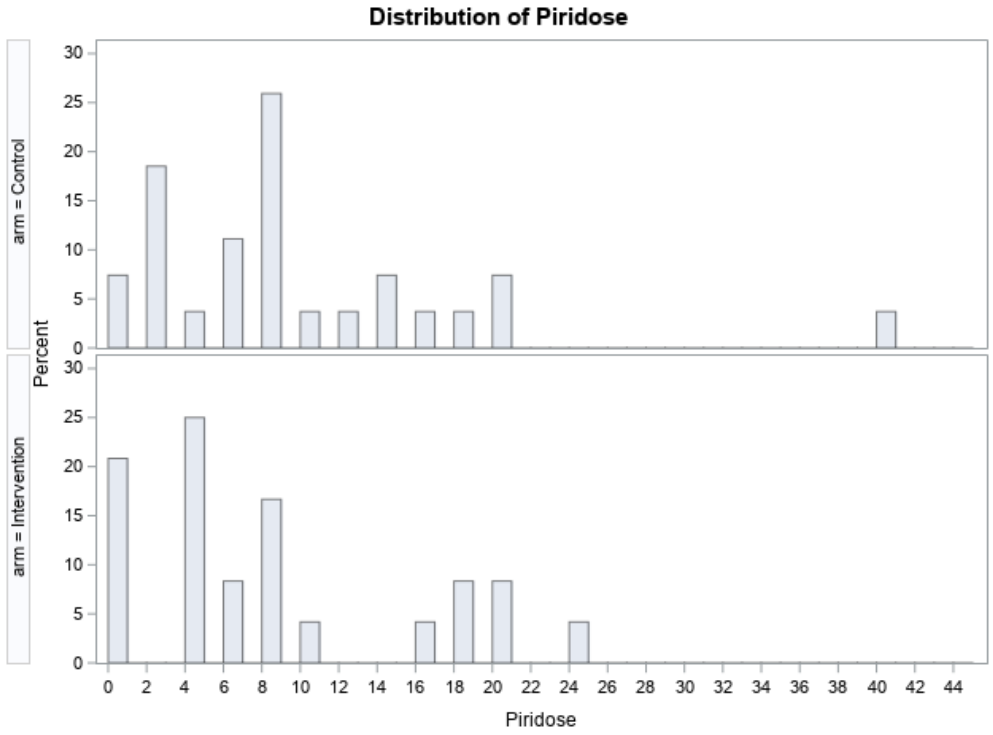
	Control arm (N = 27)	Intervention arm (N = 24)	P-value
Piritramide			
Mean ± std	9 ± 8	8 ± 7	
Median (Q1-Q3)	8 (2 to 14)	6 (4 to 13)	0.54

There is no statistical evidence for a difference in perioperative 24h piritramide consumption between intervention arm and control arm: median dose 6mg in the intervention arm compared to median 8mg in the control arm, P-value 0.54

BOXPLOT:



HISTOGRAM:



Missing data of perioperative piritramide consumption for 3 subjects in the intervention arm and for 1 subject in the control arm.

2.4 VAS score assessment during 48h post-surgery

The VAS score is available in 54 of the 55 subjects. Missing info for 1 subject in the intervention arm.

0h (when waking up) at rest (N = 54)

30min postoperatively at rest (N = 54)

1h postoperatively at rest (N = 54)

1h30 postoperatively at rest (N = 50)

2h postoperatively at rest (N = 53)

2h postoperatively during movement (N = 40)

4h postoperatively at rest (N = 54)

4h postoperatively during movement (N = 41)

6h postoperatively at rest (N = 53)

6h postoperatively during movement (N = 40)

8h postoperatively at rest (N = 51)

8h postoperatively during movement (N = 39)

24h postoperatively at rest (N = 54)

24h postoperatively during movement (N = 42)

32h postoperatively at rest (N = 48)

32h postoperatively during movement (N = 36)

48h postoperatively at rest (N = 48)

48h postoperatively during movement (N = 37)

Please note, in the first twelve subjects enrolled, no VAS score during movement have been measured.

2.4.1 Per time point

	Control (N =28)	Intervention (N = 26)	P-value
	Median (Q1-Q3)	Median (Q1-Q3)	
0h (when waking up) at rest (N = 54)	0 (0 to 2.5)	0 (0 to 0)	0.06
30min postoperatively at rest (N = 54)	2.5 (1 to 4.5)	2 (0 to 4)	0.28
1h postoperatively at rest (N = 54)	2 (0 to 2)	1.5 (0 to 3)	0.84
1h30 postoperatively at rest (N = 50)	0 (0 to 2)	0.5 (0 to 2)	0.96
2h postoperatively at rest (N = 53)	0 (0 to 2)	0 (0 to 1)	0.16
2h postoperatively during movement (N = 40)	2 (0 to 3)	1 (0 to 2)	0.31
4h postoperatively at rest (N = 54)	1 (0 to 2.5)	0 (0 to 1)	**0.03**
4h postoperatively during movement (N = 41)	1.5 (0 to 3)	1 (0 to 2)	0.24
6h postoperatively at rest (N = 53)	0 (0 to 2)	0 (0 to 1)	0.43
6h postoperatively during movement (N = 40)	1.5 (0 to 3)	1 (0 to 2)	0.45
8h postoperatively at rest (N = 51)	0 (0 to 2)	0 (0 to 1)	0.29
8h postoperatively during movement (N = 39)	1 (0 to 2)	1 (0 to 1)	0.28
24h postoperatively at rest (N = 54)	0 (0 to 1)	0 (0 to 2)	0.67
24h postoperatively during movement (N = 42)	1 (1 to 3)	1 (0.5 to 3.5)	0.90
32h postoperatively at rest (N = 48)	0 (0 to 2)	0 (0 to 1)	0.28
32h postoperatively during movement (N = 36)	1 (0 to 2.5)	1 (0 to 2)	0.74
48h postoperatively at rest (N = 48)	0 (0 to 2)	0 (0 to 1)	0.31
48h postoperatively during movement (N = 37)	0.5 (0 to 2)	2 (0 to 2)	0.29

2.4.2 Is there a difference in the area under the curve (AUC)?

In order to calculate the area under the curve, we restrict to subjects who have at least the first assessment and the last assessment, i.e.

- When assessing the VAS score at rest, restrict to subjects with both a VAS assessment when waking up, and 48h postoperatively at rest

- When assessing the VAS score during movement, restrict to subjects with both a VAS assessment at 2h postoperatively during movement and at 48h postoperatively during movement.

Cases with a missing value at intermediate time point are imputed by taking the mean of the adjacent time points.

N = 48 with AUC VAS at rest

N = 36 with AUC VAS during movement

Area under the curve	Control arm	Intervention arm	P-value
At rest (from 0h till 48h)			
N	26	22	
Mean ± std	49 ± 52	30 ± 33	
Median (Q1-Q3)	24 (0 to 177)	23 (0 to 134)	0.35
During movement (from 2h till 48h)			
N	19	17	
Mean ± std	66 ± 45	68 ± 58	0.88
Median (Q1-Q3)	45 (12 to 149)	63 (0 to 177)	

There is no statistical evidence for a difference in the area under the curve between the intervention arm and control arm: P-value 0.35 at rest and P-value 0.88 during movement.

2.4.3 Evolution during 48 h

Mixed models were applied to assess whether there is a difference in the evolution of the VAS scores over time between the intervention and the control arm. Unstructured working correlation was used in order to take into account the dependency between the several measurements of the same subject.

At rest

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	1.5502	0.2099	52	7.39	<.0001
time	-0.01673	0.006499	52	-2.57	0.0130
intervention	-0.5327	0.3026	465	-1.76	0.0790
time*intervention	0.004011	0.009488	465	0.42	0.6727

There is no statistical evidence for a difference in evolution of the VAS score over time at rest between the intervention arm and the control arm, P-value 0.67.

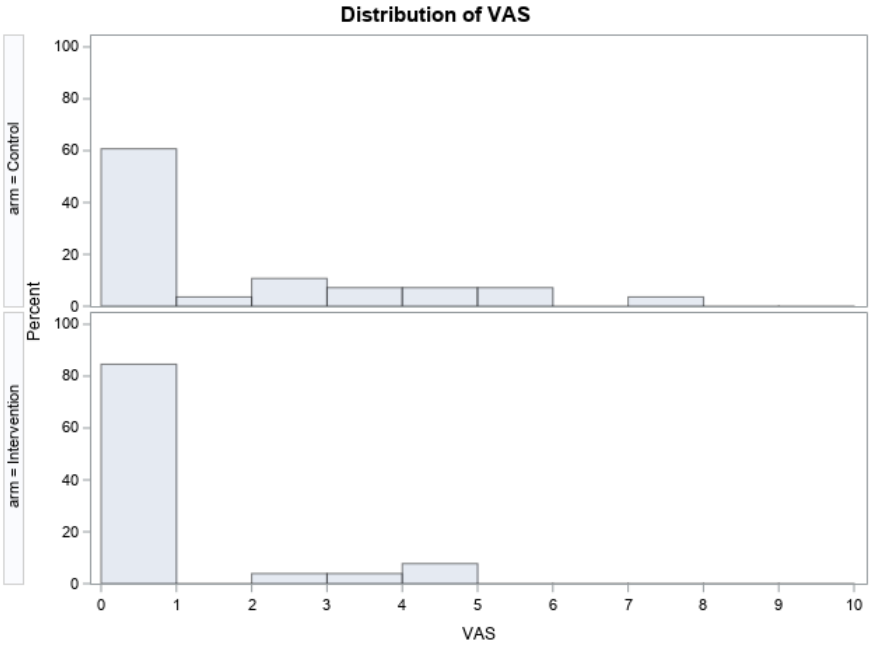
During movement

Solution for Fixed Effects					
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	1.9236	0.3474	40	5.54	<.0001
time	-0.00936	0.01030	39	-0.91	0.3688
intervention	-0.7347	0.5081	192	-1.45	0.1498
time*intervention	0.02356	0.01517	192	1.55	0.1219

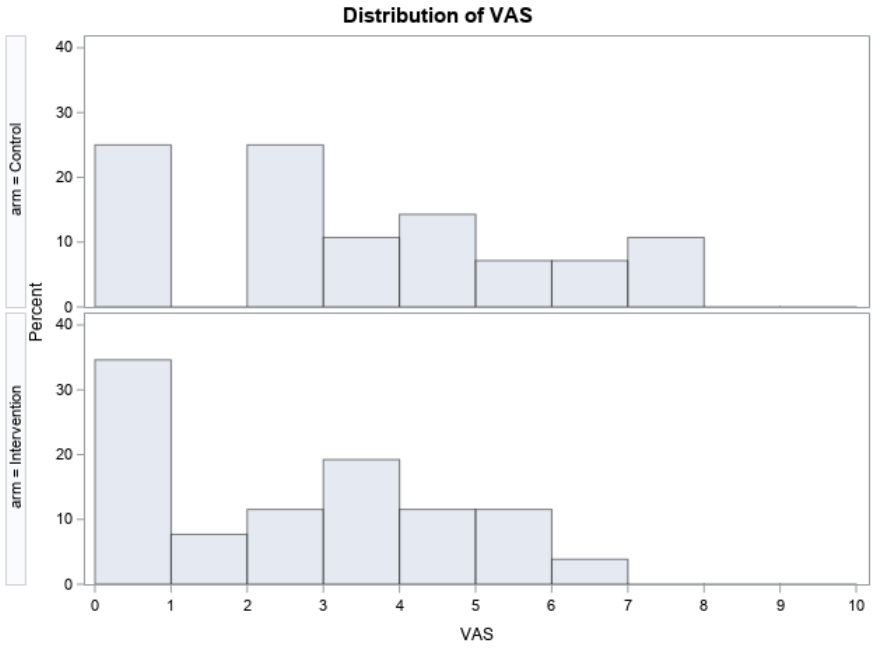
There is no statistical evidence for a difference in evolution of the VAS score over time at rest between the intervention arm and the control arm, P-value 0.12.

2.4.4 Histogram per time point

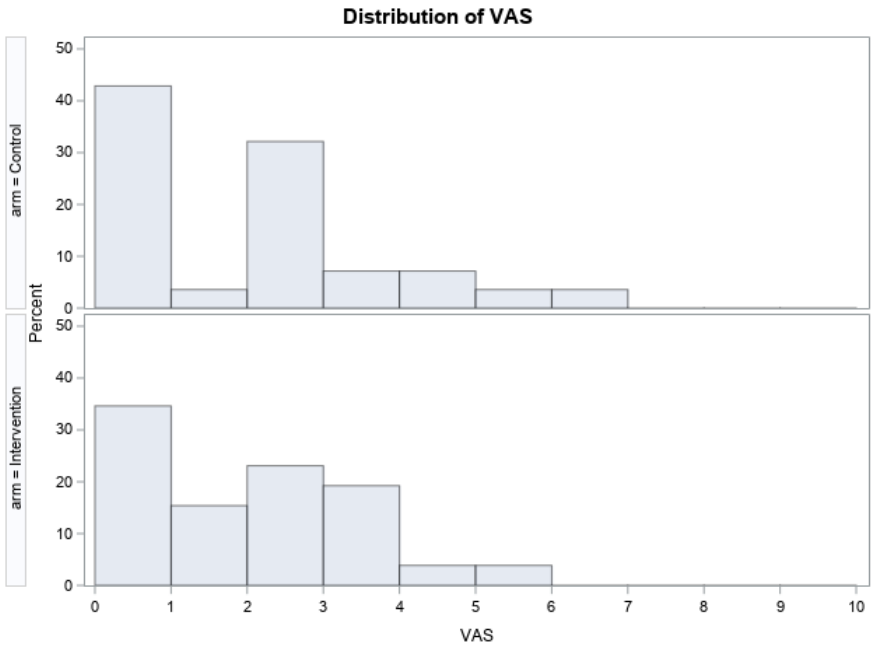
0h (when waking up) at rest (N = 54)



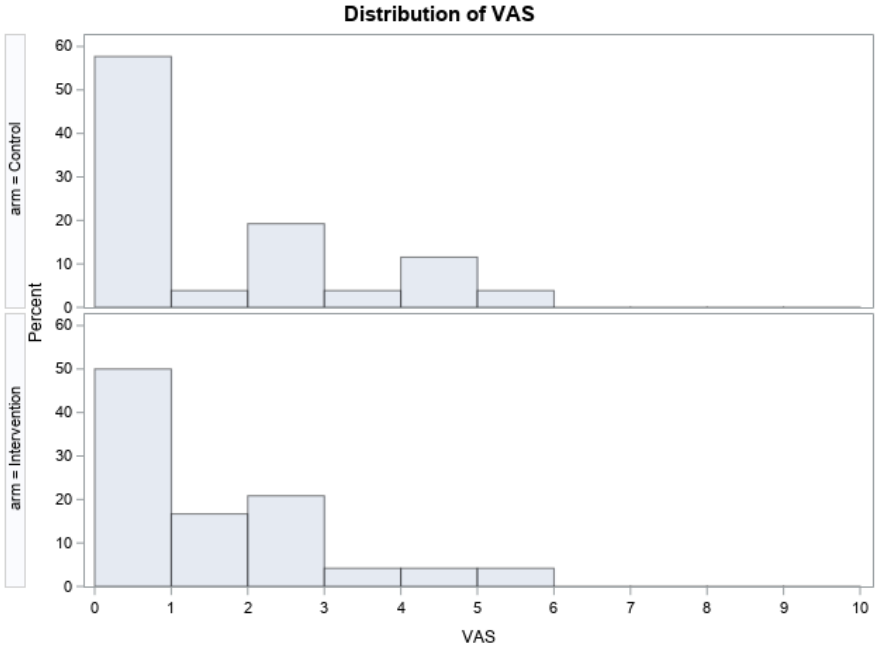
30min postoperatively at rest (N = 54)



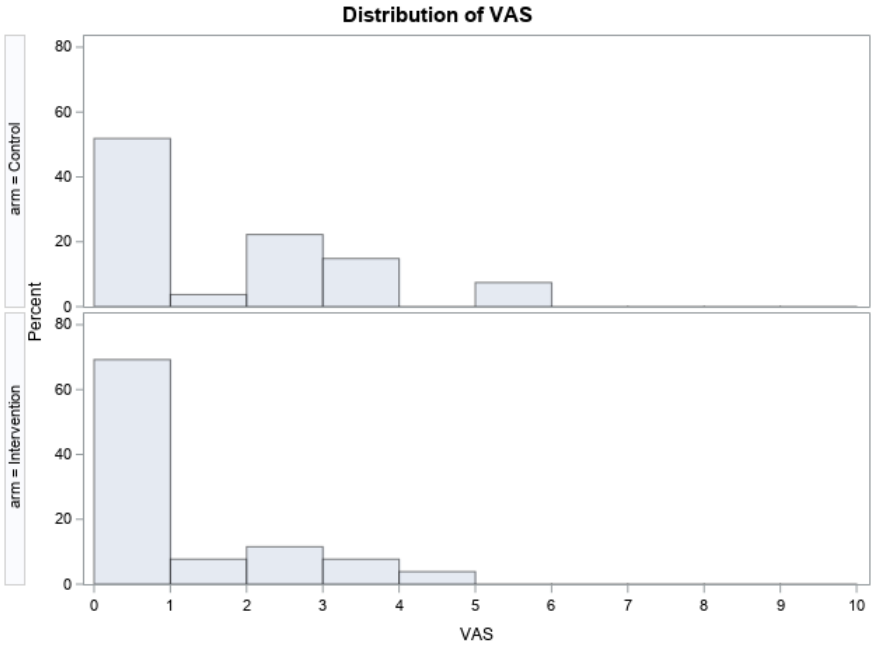
1h postoperatively at rest (N = 54)



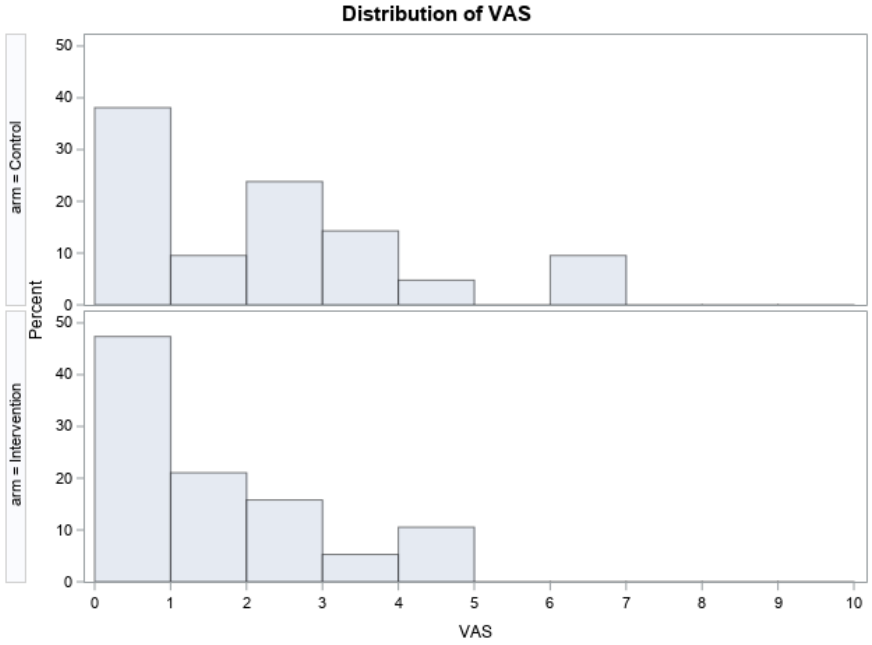
1h30 postoperatively at rest (N = 50)



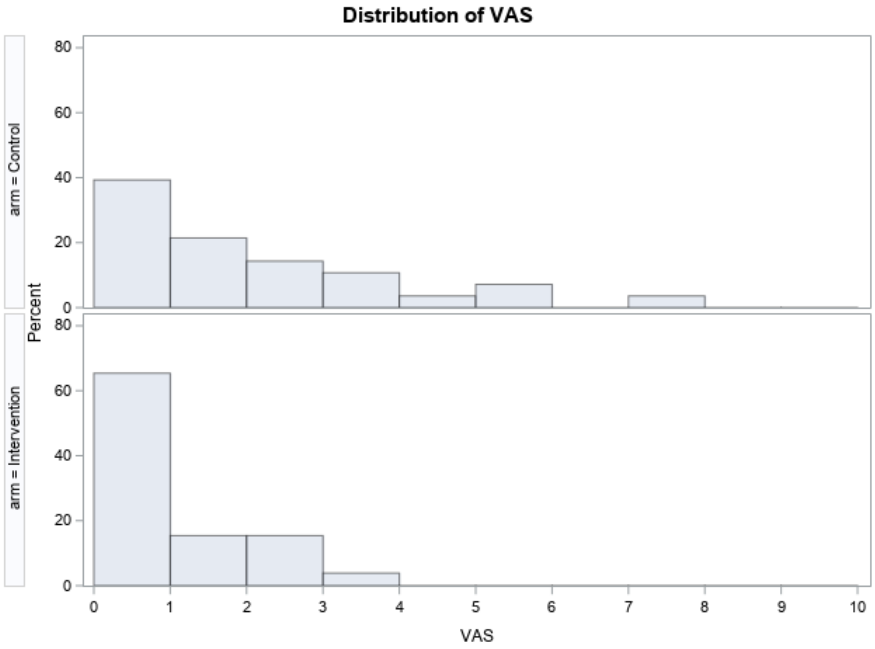
2h postoperatively at rest (N = 53)



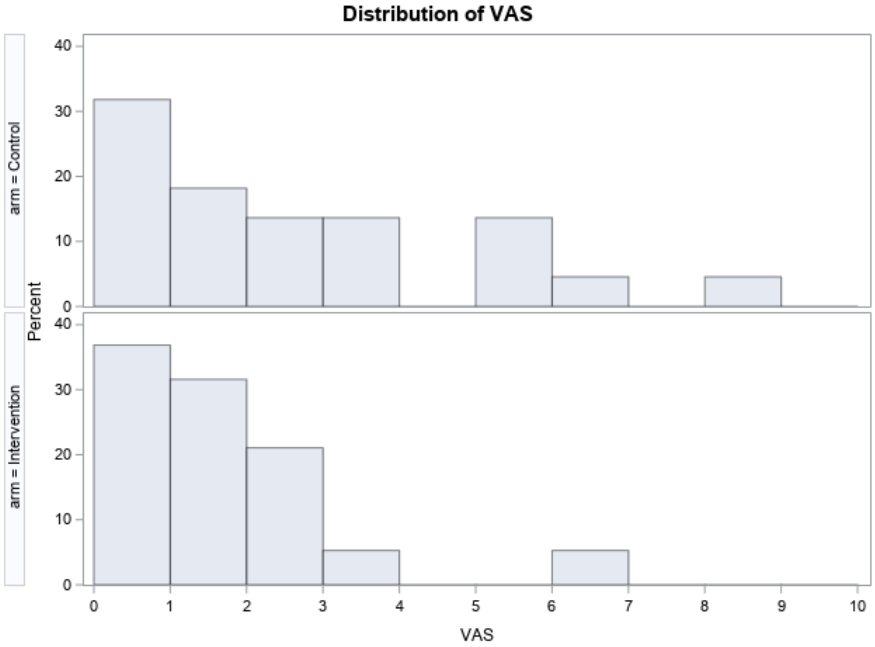
2h postoperatively during movement (N = 40)



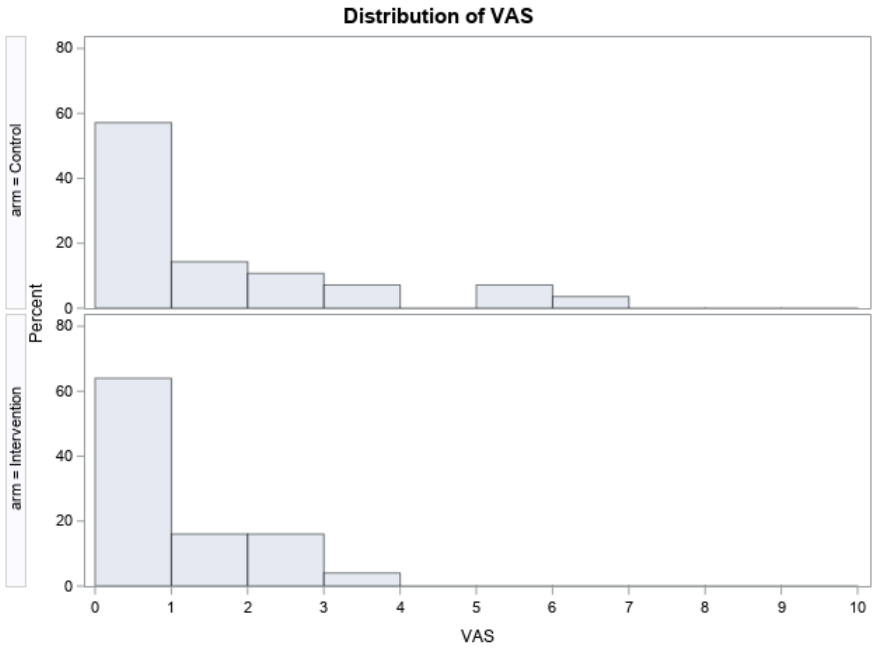
4h postoperatively at rest (N = 54)



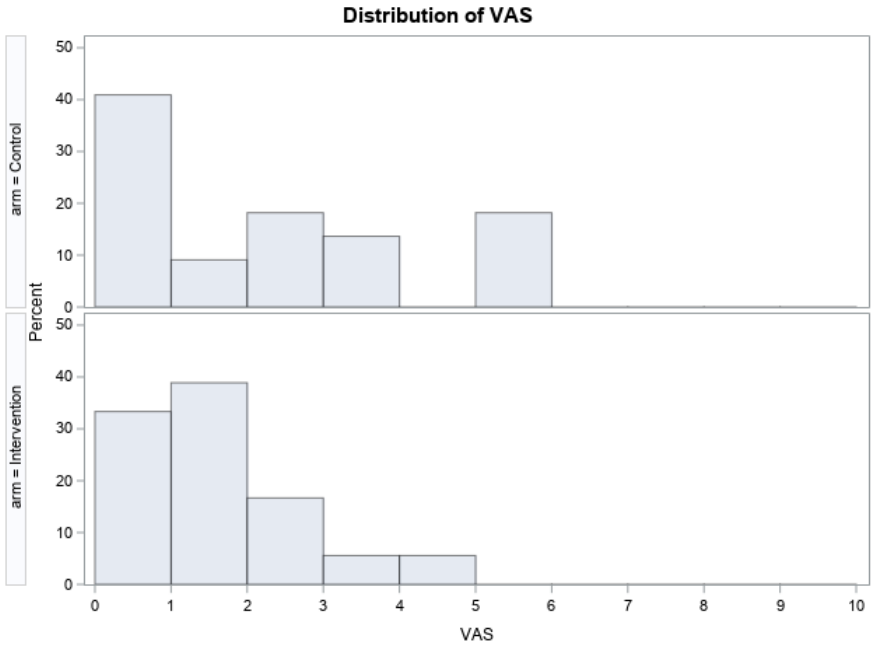
4h postoperatively during movement (N = 41)



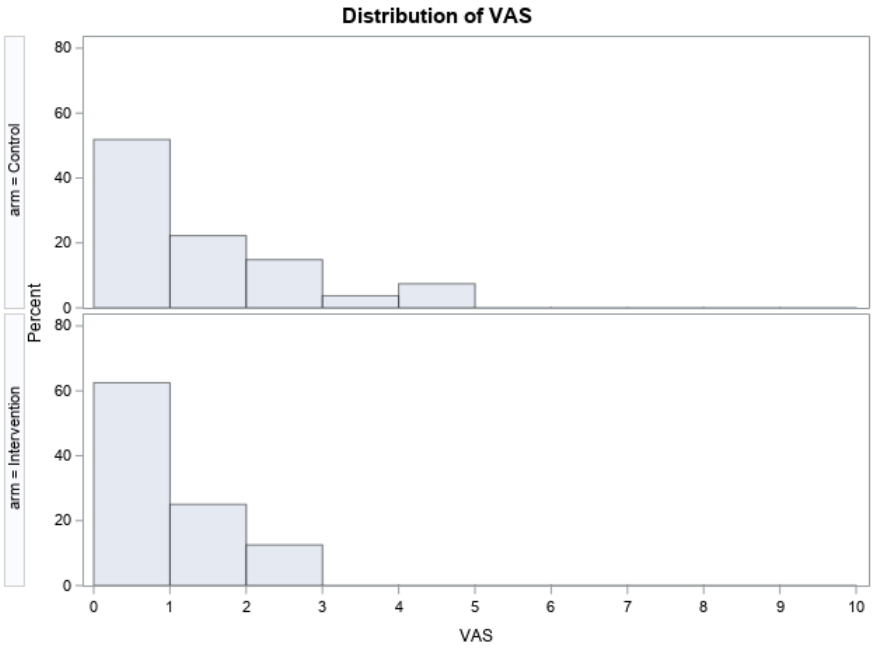
6h postoperatively at rest (N = 53)



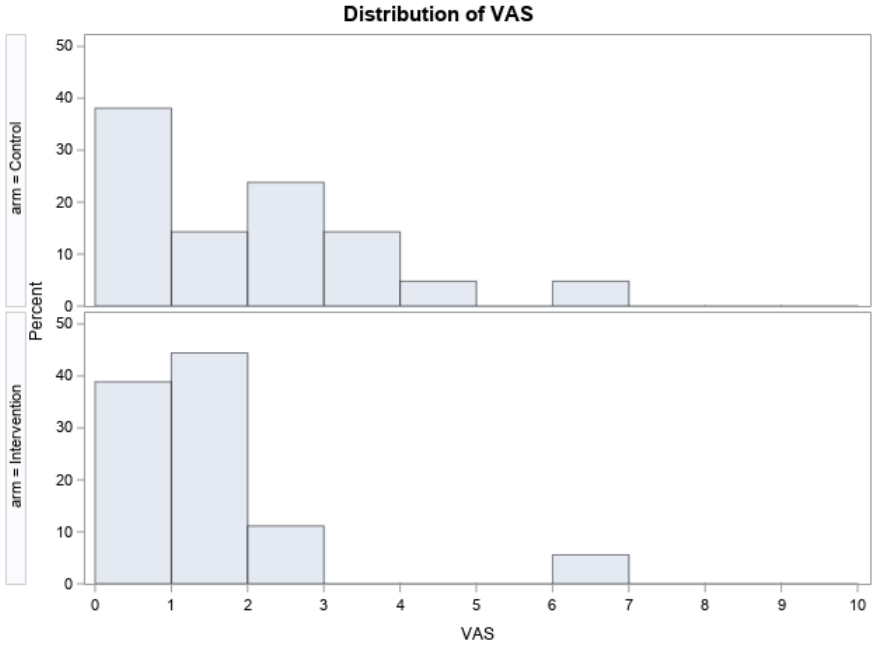
6h postoperatively during movement (N = 40)



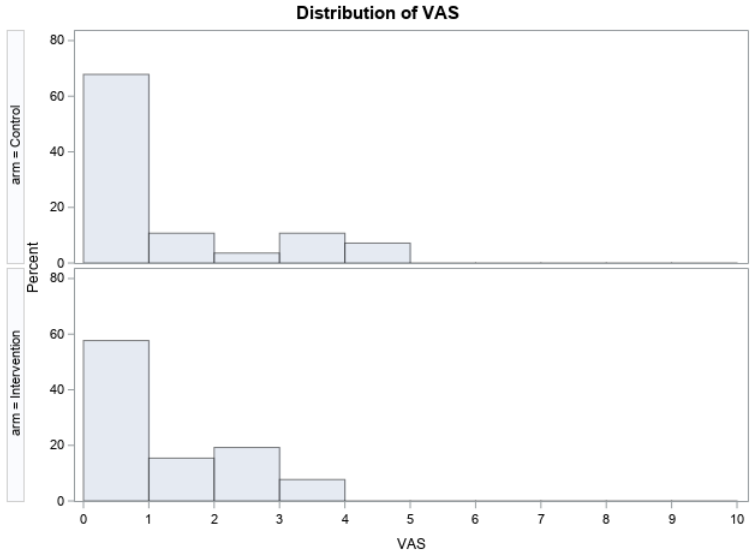
8h postoperatively at rest (N = 51)



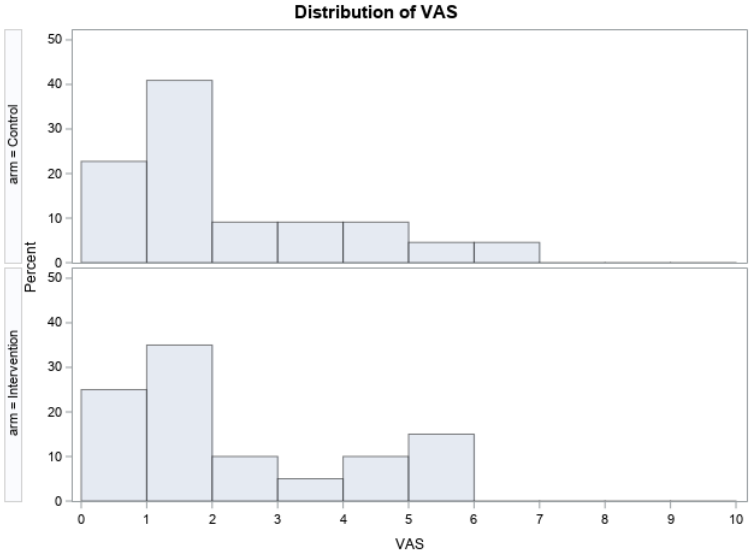
8h postoperatively during movement (N = 39)



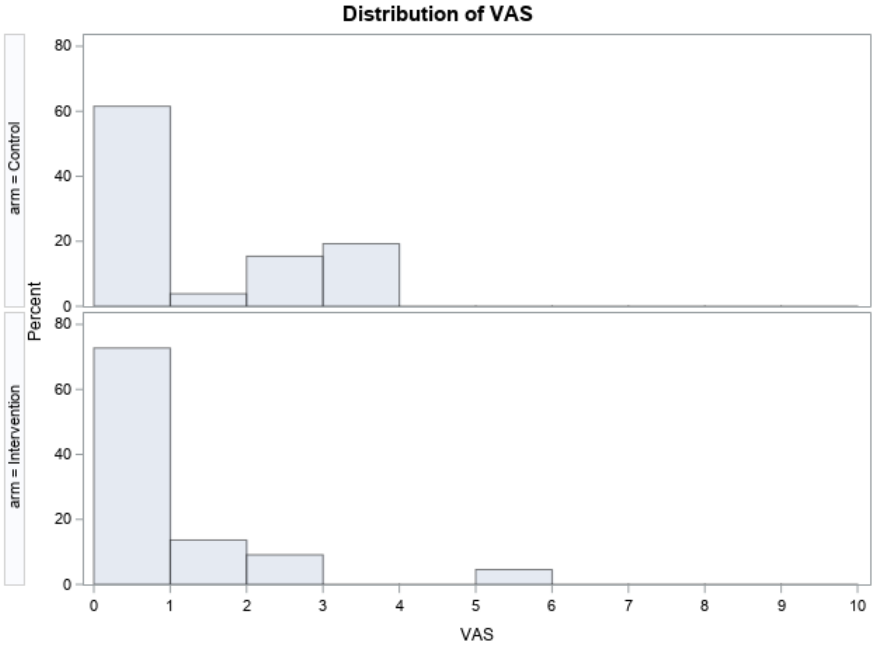
24h postoperatively at rest (N = 54)



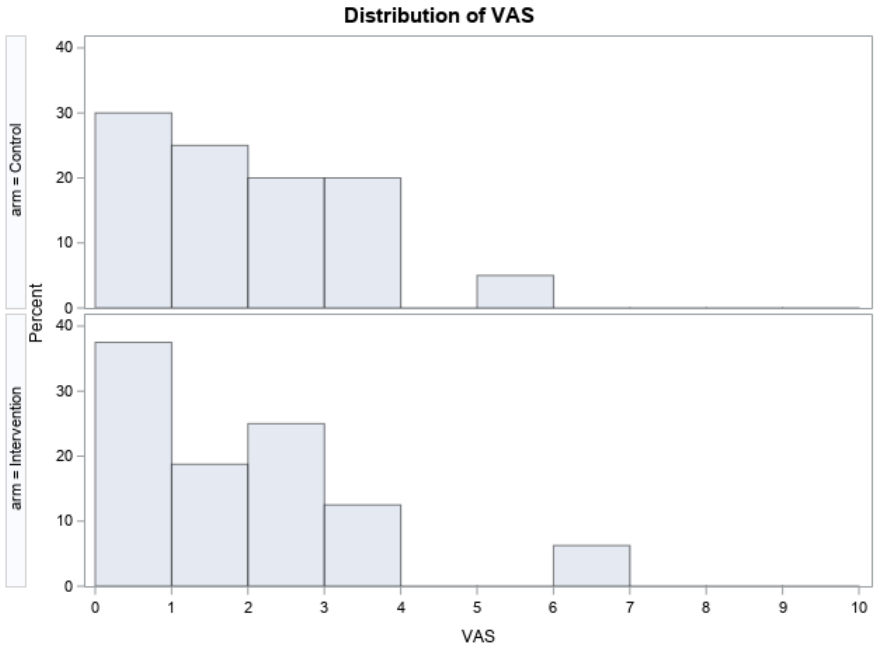
24h postoperatively during movement (N = 42)



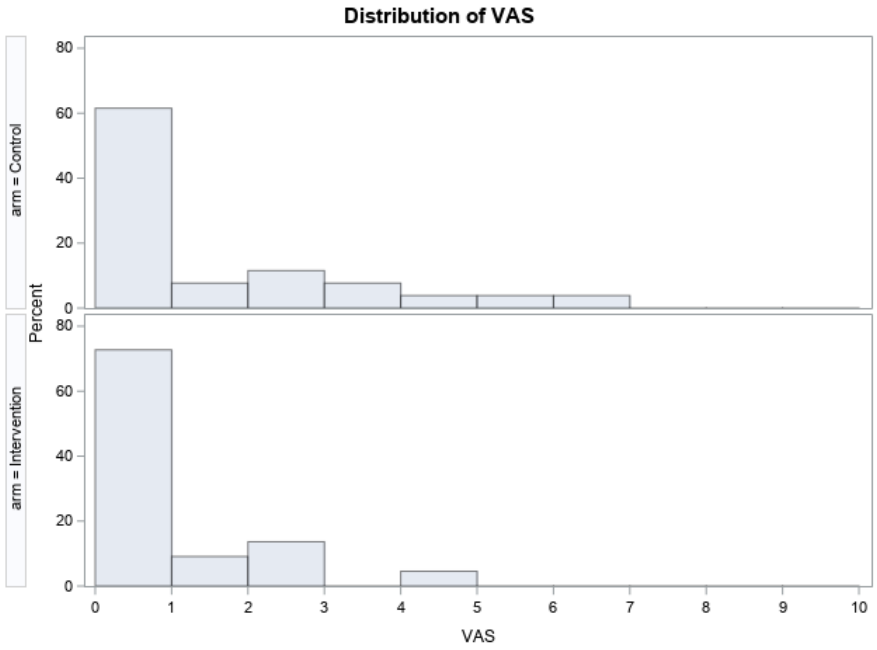
32h postoperatively at rest (N = 48)



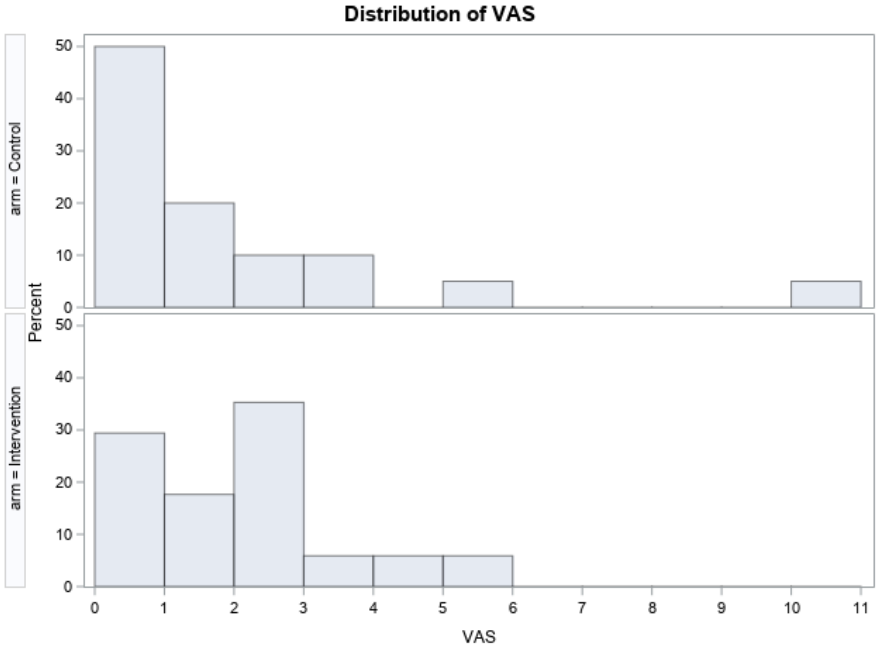
32h postoperatively during movement (N = 36)



48h postoperatively at rest (N = 48)



48h postoperatively during movement (N = 37)



2.4.5 Mc Gill questionnaire at 6 months post-surgery

54 subjects have completed the McGill questionnaire.

Two subjects have undergone surgery during the 6 months follow-up period as indicated on the form M6 physical examination. But no further info was provided on the Procedures part of the CRF. Both subjects will be excluded from the Mc Gill assessment.

N = 52

	Control arm (N = 28)	Intervention arm (N = 24)	P-value
McGill			
Mean ± std	0.7 ± 0.7	0.7 ± 0.7	
Median (Q1-Q3)	0.5 (0.1 to 1.0)	0.5 (0.3 to 1.0)	0.60

There is no statistical evidence for a difference between the intervention and control arm in terms of the McGill questionnaire at 6 months: median 0.5 in both arms, P-value 0.60.

3 SAFETY ANALYSIS

3.1 General information

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from ICF signature until up to 3 days after last administration of study treatment. After this period, only SAEs which have a reasonable possibility to be related to study treatments were collected.

Some hospitalization scenarios did not require reporting as an SAE such as:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by study medication.
- Hospitalisation planned before the subject consented for study participation and where admission did not take longer than anticipated.
- Hospitalisation for reasons described in the protocol (e.g. hospitalisation for study medication administration, hospitalisation for study related procedures). However, event requiring hospitalisation or prolongation of hospitalisation as a result of a complication of study medication administration or study related procedures will be reported as SAE.
- Hospitalisation or prolonged hospitalisation in absence of an AE (social, technical, practical reason and/or convenience admission to a hospital, palliative care, rehabilitation).

- 55 subjects were exposed to IMPs.
- No subjects were affected by serious adverse events.
- 38 subjects were affected by non-serious adverse events.

Notes:

1. The adverse event and serious adverse event assessment method was systematic.
2. The MedDRA version used for this report is the version 24.0.

3.2 Serious Adverse Events overview

No serious adverse events were reported in this trial.

3.3 Fatalities

There were no death during the study period.

3.4 Non-Serious Adverse Events

The frequency threshold for reporting non-serious adverse events is 0 %.

The table 3 and the table 4 present all non-serious adverse events sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT) in the arm “Ropivacaine 3.5 mg/ml + Clonidine 5 µg/ml” (Intervention A) and in the placebo arm (Control arm) respectively.

Table 3: Non-serious adverse event sorted by MedDRA SOC and MedRA PT in the intervention arm.

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AE occurrences causally related to IMPs**	**AE occurrences causally related to protocol surgery**
General disorders and administration site conditions				
Pain	9	9	0	9

MedDRA SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AE occurrences causally related to IMPs**	**AE occurrences causally related to protocol surgery**
Injury, poisoning and procedural complications				
Procedural pain		1 1	0	1
Seroma		4 4	0	4
Musculoskeletal and connective tissue disorders				
Pain in extremity		1 1	0	0
Vascular disorders				
Haematoma		1 1	0	1
Haemorrhage		1 1	0	1

Table 4: Non-serious adverse event sorted by MedDRA SOC and MedRA PT in the control arm.

MedDRA SOC *MeDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AE occurrences causally related to IMPs**	**AE occurrences causally related to protocol surgery**
Gastrointestinal disorders				
Nausea	1	1	0	0
General disorders and administration site conditions				
Pain	17	17	0	16
Infections and infestations				
Post procedural infection	1	1	0	1
Injury, poisoning and procedural complications				
Procedural pain	3	3	0	3
Seroma	3	3	0	3
Nervous system disorders				
Dizziness	1	1	0	0
Migraine	1	1	0	0
Vascular disorders				
Haematoma	1	1	0	1

The table 5 presents the number of subjects who presented adverse events sorted by severity, relationship and arms.

N subjects with:	**Control arm (N = 28)**		**Intervention arm (N = 27)**		**P-value**
Grade ≥1	24	86%	14	52%	0.009
Grade ≥1 related to surgery	21	75%	13	48%	0.05
Grade ≥1 unrelated surgery	4	14%	1	4%	0.35
Grade ≥3	1	4%	-	-	1
Grade ≥3 related to surgery	1	4%	-	-	1
Grade ≥3 unrelated to surgery	-	-	-	-	-

The table 6 specified the number of subjects who presented adverse events sorted by MedDRA System Organ Class and arms.

N subjects with:	**Control arm (N = 28)**		**Intervention arm (N = 27)**		**P-value**
Grade ≥1	24	86%	14	52%	0.009
Gastrointestinal disorders	1	4%	-	-	1
General disorders and administration site conditions*	17	61%	9	33%	0.06
Infections and infestations	1	4%	-	-	1
Injury, poisoning and procedural complications	6	21%	5	19%	1
Musculoskeletal and connective tissue disorders	-	-	1	4%	1
Nervous system disorders	2	7%	-	-	0.49
Vascular disorders	1	4%	1	4%	1

* All had reported “Pain”.

4 DISCUSSION

The primary outcome of this double blind placebo-controlled study was to compare the effectiveness of pecs block associated to general anaesthesia in terms of total piritramide consumption. No statistical evidence for a difference in perioperative 24hours piritramide consumption between pecs group and control group was found. Moreover, there was no statistical difference in terms of intraoperative doses of remifentanil.

The VAS score at waking up tend to be lower in the pecs group without any statistical significance but there is a statistical difference in the VAS score at 4 h post.

This finding was also reported by Kamiya and al.[7] who showed that PECS block combined with propofol-remifentanil anaesthesia significantly improved the pain score at 6h postoperatively but not remifentanil consumption.

Versyck and al.[8] in a metanalysis showed that PECS bloc II significantly reduced postoperative opioid consumption.
Compared to the studies in the metanalysis, in our study and this of Kamiya, subjects in both groups received a bolus of piritramide before wakening in addition to paracetamol and diclofenac. Moreover, we can notice that VAS score even in the group control were very low. This might explain that we didn't find a greater difference in the postoperative pain and piritramide consumption between the two groups.
The PECS II block is applied to anesthetize the breast and axilla region and involved two injections. The first injection is realized between the pectoralis major and minor muscle to block the medial ant lateral pectoral nerves. The second injection is accomplished between the pectoralis minor and the serratus anterior muscle to block intercostobrachial, intercostal III-IV-V-VI and the long thoracic nerve. Local anaesthetics cannot reach the anterior cutaneous branches of the thoracic intercostal nerves and branches of the supraclavicular nerves that may result in an inability to anesthetize the medial side of the breast region.[5,9]

There is a statistical evidence that there is less adverse event all combined in the pecs group compared to the placebo group ($p < 0.009$) and less adverse event related to the surgery (p 0.05). As we categorize the type of adverse event, the pain tend to be less in the pecs group compared to the control group (p: 0,06).

The secondary outcome was to evaluate the incidence of persistent pain 6 months after the surgery.
The McGill Pain Questionnaire (MPQ) and its short-form, the SF-MPQ are the most widely used measures of pain qualities. A revised version of the SF-MPQ, the SF-MPQ-2, has been published.[10] The SF-MPQ-2 was used to measure the qualities of pain. It includes 22 items that assess qualities of pain and the intensity of each quality on a 10-point NRS. The total score was calculated from the mean of 22 items. There is no difference in the evaluation if chronic pain with the Mc Gill questionnaire.
In this study, the anaesthesia was conducted by propofol and remifentanil. Many authors suggested that remifentanil could induce acute opioid tolerance (AOT) and opioid-induced hyperalgesia (OIH) when remifentanil is infused at ≥0.1 µg/kg/min. Hyperalgesia and increased pain in the postoperative period is now considered an essential mechanism for the development of chronic pain. [11]

There are several limitations to this study. First, due to ethical considerations we decided to use analgesic such as paracetamol, diclofenac and a bolus of piritramide in both groups before wakening that could explain the results of this study. Also, the antiemetic prophylaxis was manage following the Apfel score and dexamethasone could have analgesic effect. [12] Moreover depending on the surgeon some patients had compressive bandage around the chest wall that compress the drain inducing more pain and this bandage are removed 24 hours after the surgery.
Second, in this study patients benefited lumpectomy or mastectomy with axillary dissection. As a lumpectomy was performed we didn't consider in which quadrant of the breast the tumour was localized.
Another limitation is that the Mc Gill questionnaire was done 6 months after the surgery and more of the patients already done or were under radiotherapy treatment. Radiotherapy is known to be associated with persistent pain following breast surgery. [13]

5 CONCLUSIONS

The PECS block associated to general anaesthesia was not effective in terms of total piritramide consumption but was effective for reducing pain postoperative pain 4 hours after the surgery. There is no benefit of the PECS Block to prevent chronic pain. However the limitations of the study involves to carrying out further studies

6 ADDITIONAL INFORMATION

6.1 Global substantial protocol amendments

The global substantial amendments to the protocol are summarised in the below table.

Amendment date	Description
26/09/2016	- VAS assessments changes - Adding one exclusion criteria: subjects that require bilateral mastectomy or bilateral lumpectomy
23/10/2017	• Inclusion and exclusion criteria clarification (Adequate liver function and cardiac function assessment) • Length of study (recruitment period)
14/11/2018	• ICF amendment due to changes in European Data Privacy legislative framework
03/12/2018	• Sample size modification

Table 7: Substantial protocol amendments

6.2 Global interruption(s) and restarts

There were no global interruption to the trial.

6.3 Limitations and caveats

The limitations and caveats applicable to this summary of the results are the following:

Due to slow accrual, the sample size has been modified (protocol version 4.0): targeting a statistical power of 0.80 instead of 0.90

7 APPENDIX 1: List of participating investigators

Site	Principal investigators
Institut Jules Bordet (IJB)	Dr. Maurice Sosnowski

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