

# Acute and Chronic Pain after Shoulder Surgery: Treatment and Epidemiology

PhD dissertation

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Health  
Aarhus University  
2015

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## **Preface**

This PhD dissertation is based on research performed during my employment at the Department of Orthopedic Surgery, Horsens Regional Hospital, and my enrolment at the Department of Clinical Medicine, Aarhus University from 2011 to 2015. Part of study **I** was carried out at the Department of Orthopedic Surgery, Aarhus University Hospital.

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**Public defense:** June 10<sup>th</sup> 2015.

## Acknowledgements

I extend my deepest thanks to my supervisors Kjeld Søballe and Lone Nikolajsen for their guidance and conveyed knowledge. I am very grateful for the possibility of research training that they have provided me, and for the good cooperation that we have. Also a big thank you to my other co-authors, Birgitte Brandsborg, Peter Nørgaard Mønsted, Jan Mick Jensen, and Thomas Fichtner Bendtsen, for their ideas and critical comments. Thank you to my Head of Department, Gerhardt Teichert, for professional sparring. Also a deep-felt thank you to the other people I have been informally trained by along the way: Lise Viskum Hansen for data management, Niels Trolle and Morten Frydenberg for statistical analysis, and secretaries Helle Obenhausen Andersen and Line Jensen for proofreading manuscripts.

I wish to thank the financial contributors for making the studies possible: The Health Research Fund of Central Denmark Region (DKK 1.780.000), Augustinusfonden (DKK 100.000), The Family Hede Nielsen Foundation (DKK 74.500), The Danish Rheumatism Association (DKK 50.000), and Horsens Regional Hospital (DKK 40.000 and the necessary, but unused, deficit guarantee for my salary). Office facilities and supplies were provided by Horsens Regional Hospital and Aarhus University Hospital, and finances were administrated by Horsens Regional Hospital.

Warm thanks go to my colleagues at the Research Unit of Horsens Regional Hospital and the Clinical Orthopedic Research Group of Aarhus University Hospital for professional and friendly support over the years. Thanks to my hired help: the project nurses Gitte Ellemose Vinther, Johanna Strohbach, and Mette Blichfeldt Kofod for inclusion and data collection during my maternity leave, research assistant Ronja Tügel Carstensen for digitalizing the large majority of the many hundred questionnaires, and project nurse Rie Espensen for insights into the inclusion process.

Heartfelt thanks to my entire family for love, support and inspiration in every way.

Especially, I extend my thanks to the patients for their willingness to contribute personally to our work to attain new knowledge, and to the involved staff at Horsens Regional Hospital and Aarhus University Hospital for their insistent efforts to do, and to improve, “the best we know how”.

Horsens, February 2015

## List of papers

- I.** Bjørnholdt KT, Jensen JM, Bendtsen TF, Søballe K, Nikolajsen L.  
Local infiltration analgesia versus continuous interscalene brachial plexus block for shoulder replacement pain: A randomized clinical trial. Submitted.
- II.** Bjørnholdt KT, Mønsted PN, Søballe K, Nikolajsen L.  
Dexamethasone for pain after outpatient shoulder surgery: a randomised, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand.* 2014 Jul; 58(6): 751-758.
- III.** Bjørnholdt KT, Brandsborg B, Søballe K, Nikolajsen L.  
Persistent pain is common 1–2 years after shoulder replacement. A nationwide registry-based questionnaire study of 538 patients. *Acta Orthop.* 2015 Feb; 86(1): 71-77.

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## List of abbreviations and definitions

ACR	Acromio-clavicular joint resection
ASD	Arthroscopic subacromial decompression
DSR	Danish Shoulder Arthroplasty Register
GCP	Good clinical practice (international guideline)
ISB	Interscalene brachial plexus block
ISC	Interscalene brachial plexus catheter
LIA	Local infiltration analgesia
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
PACU	Postoperative care unit
PCA	Patient-controlled analgesia
RCT	Randomized controlled trial
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VAS	Visual analog scale

**Definitions** from the IASP (International Association for the Study of Pain 2012), unless otherwise stated.

Analgesia: Absence of pain in response to stimulation which would normally be painful.

Chronic postoperative pain: Pain developed after a surgical procedure, lasting at least 2 months (or beyond the usual healing period), not caused by anything other than surgery (e.g. continuing malignancy or chronic infection) and not attributable to a pre-existing problem (Macrae 1999).

Hyperalgesia: Increased pain from a stimulus that normally provokes pain.

Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Paresthesia: An abnormal sensation, whether spontaneous or evoked.

Sensitization: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.

## Overview of studies

	Study I	Study II	Study III
	Local infiltration analgesia versus continuous interscalene brachial plexus block for shoulder replacement pain: A randomized clinical trial <i>Submitted</i>	Dexamethasone for pain after outpatient shoulder surgery: a randomized, double-blind, placebo-controlled trial <i>Acta Anaesthesiol Scand 2014 Jul; 58(6): 751–758</i>	Persistent pain is common 1–2 years after shoulder replacement. A nationwide registry-based questionnaire study of 538 patients <i>Acta Orthopaedica 2015 Feb; 86 (1): 71-77</i>
Question	Does LIA provide more effective analgesia after shoulder replacement compared to ISC, assessed by opioid consumption and pain intensity?	Does 40 mg dexamethasone significantly improve analgesia after ASD and/or ACR compared to 8 mg, assessed by pain intensity and analgesic consumption?	What are the prevalence of, the characteristics of, and risk factors for persistent shoulder pain 1–2 years after shoulder replacement?
Patients	69 shoulder replacement patients from two Danish hospitals were randomized. 61 patients were available for analysis.	101 ASD/ACR patients from Horsens Regional Hospital in Denmark were randomized. 73 patients were available for analysis.	786 patients were registered in the Danish Shoulder Arthroplasty Register. 538 patients were available for analysis.
Methods	RCT. Patients were randomized to LIA or ISC. Outcome measures were analgesic use, pain intensity, and side effects for 3 days, and complications for 3 months.	Blinded RCT. Patients were randomized to dexamethasone 40 mg, 8 mg or placebo. Outcome measures were pain intensity, analgesic use, and side effects for 3 days, and complications for 2 months.	Cohort study. A postal questionnaire was combined with registry data for descriptive statistics and multivariate logistic regression.
Results	Opioid consumption and pain scores were significantly higher in the LIA group on the day of surgery.	There was a dose-response relationship, but no significantly reduced pain intensity or analgesic use was found between the 40 mg and 8 mg groups.	22 % experienced substantial daily persistent pain. 13 % were screened positive for neuropathic pain. Severe acute postoperative pain was one of the risk factors.
Interpretation	The described LIA technique is not recommended, but problems with the ISC prompt further studies into pain management after shoulder replacement.	Increasing the dexamethasone dose does not decrease pain significantly in a multimodal analgesic regimen in these patients.	Persistent pain is a daily burden for many patients. The causes and the possibility of prophylaxis should be pursued, and patients should be followed to improve their pain management.

## Introduction

The purpose of orthopedic surgery is to alleviate pain and improve function. The aim of this PhD dissertation is to focus on pain alleviation after shoulder surgery, and to study the treatment of acute postoperative pain and the epidemiology of chronic postoperative pain. This work was done in order to provide a basis for further research and improve the treatment available to patients.

As the efficacy and safety of surgery increases, surgery is an option for a broader group of patients. This in combination with longer life expectancy leads to more surgery being performed, and this applies to shoulder surgery as well. There were 16,720 shoulder operations in 2010 in Denmark (population of 5.5 million (Danmarks Statistik 2010)), and of these 8,209 were performed as outpatient surgery and 8,511 were performed as in-patient surgery (Danske Regioner 2011).

As the number of surgical patients has increased, the length of stay in hospital has diminished. Over the last 15-20 years, there has been a shift toward ambulatory surgery and early discharge after major surgery (“fast track” surgery). This requires patients to self-manage their pain, as pain treatment is commenced or continued away from the care of professionals. Still, the experience and knowledge necessary to make the required assessments and adjustments must be available to patients. Early discharge amplifies the importance of safe, simple, and effective pain treatment that allows for easy transition to the home (Jakobsson 2014). Optimal postoperative pain treatment improves patient comfort and well-being (quality of life); reduces complications; permits sleep, eating, and exercises (minimizing loss of strength and range of motion); and thus is a key factor to a speedy recovery (Kehlet 2002, Carli 2011). The first two studies of this PhD dissertation aim to improve the management of acute postoperative pain in major and minor shoulder surgery.

Quality assessment must be undertaken in order to determine whether the surgery performed has the desired effect. The effect of shoulder replacement is often assessed by patient-reported outcomes (a composite score) and revision rates, which are compiled in the national Danish Shoulder Arthroplasty Register. However, the postoperative occurrence and characteristics of pain should be more closely examined. The prevalence of chronic postsurgical pain after other operations has been found to be quite high, and focus on this problem will hopefully lead to improved surgical outcomes. The third study of this PhD dissertation focuses on the epidemiology of persistent pain after shoulder replacement, supplementing the registry data with a patient questionnaire.

## Background

This review introduces the reader to the following: acute postoperative pain, the two surgical procedures involved in studies **I** and **II**, currently used methods of pain treatment after shoulder surgery, the two interventions in studies **I** and **II** (local infiltration analgesia and dexamethasone), and chronic postoperative pain pertaining particularly to shoulder replacement. The literature search has been performed in PubMed, Web of Science, and in the references of selected articles.

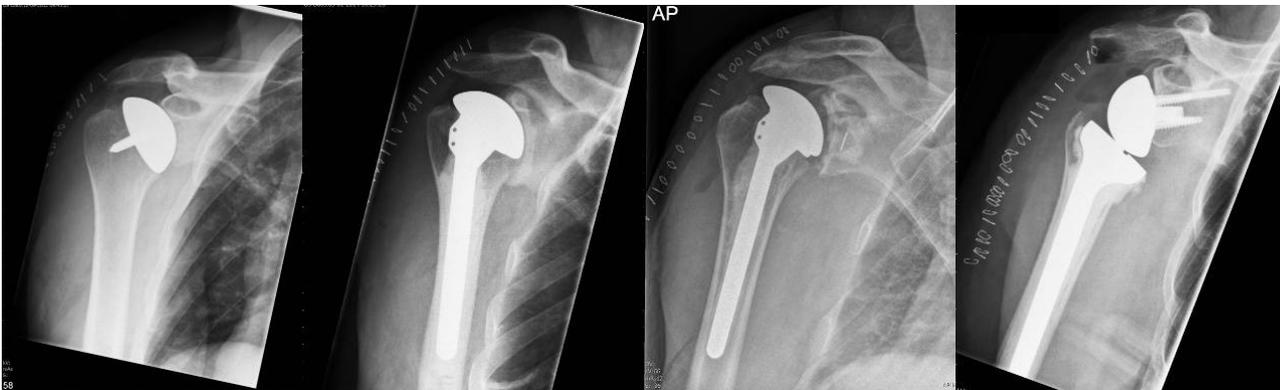
### Acute postoperative pain

Acute postoperative pain commences at the end of surgery and resolves during the healing period, usually less than 3 months, depending on the type of surgery (Werner 2014). The pain is generally most intense during the first 1-3 days, and then gradually decreases over the healing period, although it is exacerbated by touch (as during changes of dressings), reflex muscle spasm, specific movements, and localized complications (infection, hematoma, rupture/fracture of involved structures, loosening/failure/malpositioning of implanted devices). In clinical studies, even with highly selected and seemingly homogeneous patients and treatment, postoperative pain intensity shows a very large variation between patients (Bullingham 1984, Weber 2007). This is due to difficulty in measuring pain, as well as a true difference in pain intensity between patients (Frey-Law 2013, Reed 2014). Due to a multitude of bio-psycho-social factors, some of which have been identified, pain experience is very individual and still cannot be easily predicted (Weber 2007, McLean 2013, Phillips 2014). Despite increased focus over the past decades, recent reports illustrate the continuing problem of insufficiently treated acute postoperative pain (Gerbershagen 2013), especially in shoulder patients (Lindberg 2013).

The physiology of pain is intricate, but a very brief summary is presented here to serve as background for the treatment of pain described later. Nociceptors (primary afferent nerve fibers that respond to noxious stimuli) are activated by mechanical stimuli (dissection, instrumentation, and handling) and occasionally thermal stimuli (electrocoagulation). Pain also arises due to spontaneous firing in the afferent nerve fibers unavoidably severed or strained during surgery. This immediate peripheral sensory input is followed within minutes to hours by primary hyperalgesia: peripheral sensitization of nociceptors caused by local inflammatory mediators, consisting of lowered thresholds to stimulation, increased response to supra-threshold stimuli, and an expanded receptive field. This is adjoined by secondary hyperalgesia: enhanced response to stimuli in the surrounding uninjured tissue caused by central sensitization (changes due to massive input to the spinal cord and

brain) (Meyer 2006). Systemic effects of pain are numerous and include augmentation of the catabolic surgical stress response with hormonal changes (including increases in cortisol), and greater sympathetic activity, resulting in increased heart rate and blood pressure, reduced skin blood flow, and sweating (Coda 2001). This normal, self-limiting response to surgery is the same as to other injuries, and serves to protect us by alerting us to avoid further harm and to allow for restitution. However, alleviating postoperative pain, while supporting behavior which facilitates restitution, is an integral part of surgery, as is anesthesia.

**Figure 1. X-ray images of four types of shoulder replacement: Resurfacing, hemi-arthroplasty, total arthroplasty and reverse replacement.**



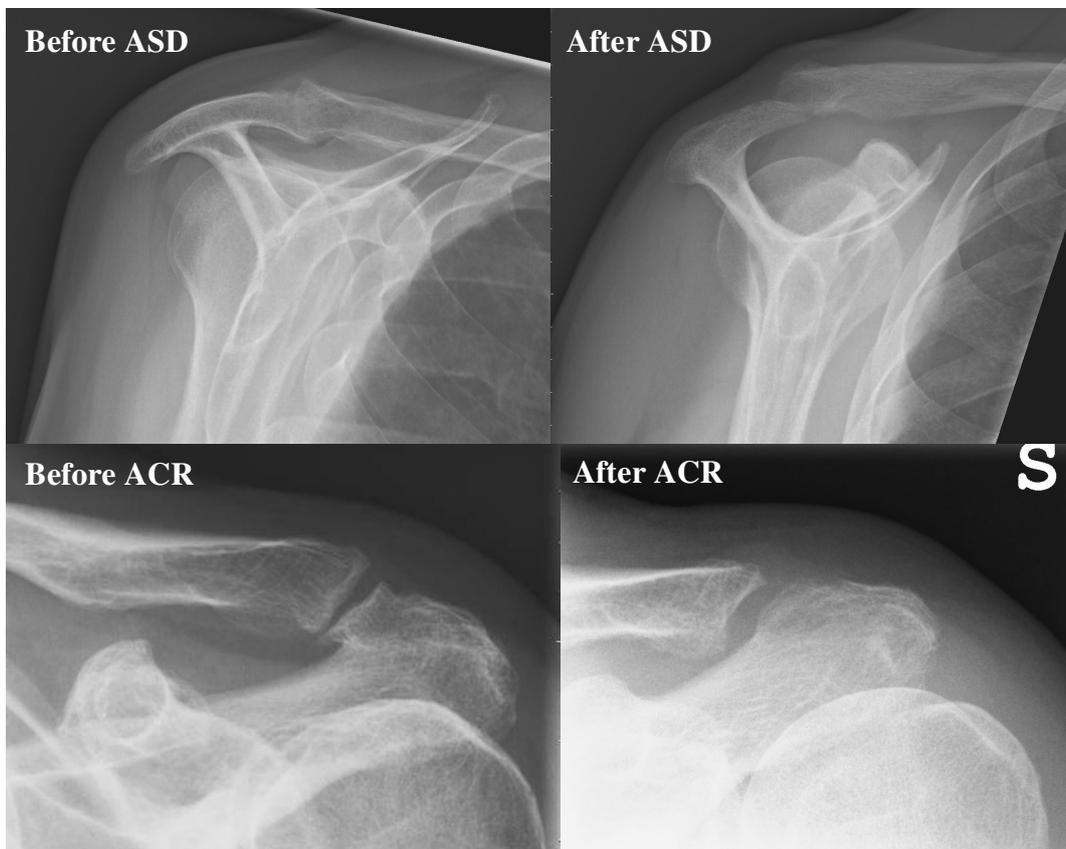
*Source: Horsens Regional Hospital.*

### **Description of the surgical procedures**

Arthroplasty or replacement of the shoulder joint is a major operation. There are four types of replacement as shown in Figure 1. In a **resurfacing** shoulder replacement, the surface of the humeral head is replaced by a metal prosthesis. In a **hemi-arthroplasty** (also known as a humeral head replacement), the humeral head is removed and replaced by a stemmed prosthesis, and in a **total arthroplasty**, the stemmed humeral head replacement is supplemented with a glenoid replacement, often made out of polyethylene. Finally, in a **reverse** shoulder replacement, the glenoid is replaced by a convex articular surface and the humeral head is replaced by a concave articular surface. The operation involves subscapularis tenotomy and reinsertion (as the most common approach), and dislocation of the shoulder joint. The operation entails intense pain lasting for days (Sripada 2012). In Denmark, just above 1000 primary and 170 secondary (revision) shoulder replacements are performed annually (Dansk Skulderalloplastik Register 2014).

Some of the most frequent outpatient shoulder operations are arthroscopic subacromial decompression (ASD) and acromio-clavicular joint resection (ACR) (Figure 2). ASD is offered to patients experiencing impingement of the rotator cuff under a curved acromion if conservative treatment has proved unsuccessful. The operation consists of resecting the bony spur on the anteroinferior side of the acromion and release of the coraco-acromial ligament to increase the amount of subacromial space and improve congruency, thereby avoiding further impingement. ACR is performed if patients instead, or concurrently, suffer from painful osteoarthritis of the acromio-clavicular joint. During this procedure, the lateral 0.5 to 1 cm of the clavicle is resected. The operation can be performed as an arthroscopic or open procedure, but as postoperative pain intensity differs according to modality (Duindam 2014), only arthroscopic procedures were examined in study II. ASD and arthroscopic ACR are quite uniform procedures, and a similar degree of pain is found postoperatively. Still, acute postoperative pain intensity ranges from none to severe, but is most often moderate (Trompeter 2010).

**Figure 2. X-ray images of patients before and after undergoing arthroscopic subacromial decompression (ASD) and acromioclavicular joint resection (ACR).**



*Source: Arhus University Hospital.*

### **Pain treatment after shoulder surgery**

*Nociceptive input* is the target of pain management strategies such as local/regional/systemic drugs, minimally invasive surgery, immobilization, cooling, compression, and patient positioning, whereas *patient experience* is the target of strategies such as patient education, social support, and cognitive/behavioral methods.

Pain treatment after shoulder surgery often involves the use of local anesthetics in order to minimize the need for systemic opioid, as pain is often severe. The shoulder is innervated by the subscapular, axillary, lateral pectoral, and suprascapular nerves from the brachial plexus (Aszmann 1996). The density of nerve endings is highest in areas where proprioception and protective reflex actions are important, such as the rotator cuff and joint capsule (Dean 2013). Interscalene brachial plexus block (ISB) is recommended for postoperative analgesia by several reviews, as it affects all involved nerves in one procedure (Borgeat 2002, Fredrickson 2010, Sripada 2012). A Cochrane review from 2014 comparing ISB to intravenous morphine for major shoulder surgery found only two trials, as ISB was often compared to other uses of local anesthetics (Ullah 2014). This illustrates the widespread acceptance of the necessity of some sort of nerve block.

Although ISB is effective in providing pain relief, it is associated with some side effects and complications. Hemidiaphragmatic paresis (phrenic nerve palsy) is common, although ultrasound guidance and lower volumes of local anesthetic may reduce this side effect from 100 % to 45 % (Sripada 2012), with 3 % of patients experiencing dyspnea for a mean of 2 days (Liu 2010). Other frequent side effects are hoarseness (recurrent laryngeal nerve palsy), experienced by 11 % for a mean of 2 days (Liu 2010), and Horner syndrome (ptosis, miosis, and anhidrosis due to sympathetic trunk affection), which may go unnoticed by patients and staff. Contraindications to the block include [1] low respiratory capacity (i.e. chronic obstructive pulmonary disease), [2] any neurological compromise which could be “first crush” (Koff 2008)(i.e. thoracic outlet syndrome, multiple sclerosis, cervical disc disease with radiculopathy, any neuropathy, or brachial plexopathy), [3] infection at the block site, and [4] coagulopathy (which could increase risk of hematoma or bleeding) (Singh 2012). Case reports of death, quadriplegia, and other very serious complications have been published (Edde 1977, Benumof 2000, Lenters 2007, Mostafa 2013), but in these cases, blocks were placed without ultrasound guidance. Safety studies of ultrasound-guided

ISB (Liu 2010, Singh 2012) reveal a prevalence of 0.8 to 0.9 % of patients with postoperative neurological symptoms attributable to the block lasting up to 3-4 months, and fewer being permanent. A fraction of these cases may instead be related to sling immobilization or the surgery itself (i.e. the necessary dislocation of the shoulder during a replacement causing traction of the brachial plexus). Other very rare complications include local infection, pneumothorax, intravascular injection, arrhythmias, and seizures (Neal 2009, Liu 2010, Singh 2012). Apart from ultrasound guidance, success rate and complication rate are dependent on training, experience, and case exposure (Fredrickson 2010).

The addition of an indwelling catheter for continuous infusion (interscalene catheter, ISC) is also technically very challenging, but it is recommended as a gold standard for major surgery such as shoulder replacement (Fredrickson 2010). The single shot effect lasts for about 8-12 hours when bupivacaine or ropivacaine is used, whereas the indwelling catheter can prolong analgesia for days (Borgeat 2002). In very experienced hands, ISC has very few long-lasting neurologic complications (6 of 659 patients, that is 0.9 % as with ISB) (Fredrickson 2009), but in average practice, complications are probably slightly more frequent than with ISB. The catheter is susceptible to dislodgement due to movement of the head and neck or incidental catching of the catheter and infusion pump. The use of a catheter postpones the transition to reliance entirely on oral analgesics until patients are discharged. Managing the catheter and the transition to oral analgesics at home requires self-efficacious patients (or help in the home), careful patient education, and good possibilities for patients to make any necessary contacts to hospital staff.

An alternative approach to ISB or ISC could be ultrasound-guided supraclavicular block, which may be safer but is less widely used (Conroy 2011). Disagreement exists as to whether even minor shoulder surgery warrants the use of ISB, or ISC, as the risk-to-benefit is less clear. Pain following minor surgery not involving the rotator cuff can be managed with suprascapular nerve block combined with axillaris nerve block or subacromial and intraarticular injection (Checcucci 2008, Price 2008, Fontana 2009). Local practice may be determined in part by case exposure and available experience.

Regardless of the placement of local anesthetic, patients often require supplementary analgesics (Fredrickson 2010), making local anesthetic only one part of a multimodal analgesic approach. For

minor shoulder surgery not involving the rotator cuff (other than arthroscopic access), supplementary acetaminophen and NSAID may be enough, but opioids may also be required, especially on the day of operation (Stiglitz 2011). For major shoulder surgery (involving the rotator cuff), opioids will be required for the large majority of patients for several days. Local cooling (Speer 1996, Singh 2001) and patient education are also often a part of the analgesic treatment.

### **Local infiltration analgesia**

Extensive periarticular infiltration with high-volume local anesthetics for postoperative analgesia after joint replacements was first described by Beard et al. in 2002 (Beard 2002) for uni-compartmental knee replacements, based on the method developed by Kerr and Kohan (Kerr 2008). The method is an alternative to the previously recommended epidural or peripheral nerve block after total hip arthroplasty (THA) and total knee arthroplasty (TKA) (Fischer 2005, Fischer 2008). In the original method, ropivacaine 300 mg, ketorolac 30 mg, and epinephrine 0.5 mg (in saline, for a total volume of approximately 150 ml) is infiltrated systematically by the surgeon throughout the surgical field, followed by postoperative injections through an intraarticular catheter (Toftdahl 2007, Kerr 2008). Since then more than 50 randomized controlled trials have been performed involving LIA for TKA and THA. The applied methods differ with regard to the solution used: ropivacaine or bupivacaine, possibly with the addition of epinephrine, ketorolac, morphine, magnesium, and/or a corticosteroid. The largest dose infiltrated is 450 mg ropivacaine, in a study of bilateral TKA (Andersen 2010). The volumes used range from 40 to 200 ml. Descriptions differ as to how the solution is infiltrated, not least with regard to how thorough a description is provided. The intra-operative infiltration can be supplemented with postoperative infusion, or one or more injections, which can be made through a catheter placed subcutaneously, intraarticularly, or perhaps better intracapsularly (Andersen 2010).

A recent meta-analysis of LIA for TKA (Xu 2014) included studies of LIA but also simple intraarticular injections of low-volume local anesthetics (limiting conclusions on the LIA technique), and only included studies with single administrations (no local catheter). For THA, a recent meta-analysis included studies with LIA both with and without a local catheter, and found an effect at 4 hours but not clearly at 24 hours, although three of the four studies using a knee catheter were positive (Yin 2014). A review by Andersen et al. 2014 (Andersen 2014) describes many of the studies, both with and without risk of bias, and finds support for the use of LIA for TKA. For THA, only two studies were found to have low risk of bias, and recommendations were not so clear, as

pain was less intense and systemic administration of multimodal analgesics could be preferred. The postoperative use of a local catheter could not be unreservedly recommended because the effect of the catheter injections had not been evaluated separately in most trials, although analgesia was noted for up to 72 hours after surgery when a catheter was used (Andersen 2014). A British meta-analysis (Marques 2014) based on data from articles and elaborative correspondence with authors found LIA to be effective for both TKA and THA, although the risk of bias and lack of uniform methodology between studies were also mentioned here as limiting factors in providing more solid conclusions.

The technique of LIA has not previously been used in shoulder replacement. When the LIA method used in previous studies of THA and TKA is adjusted for use in shoulder replacement, many choices must be made. Ropivacaine is preferred to bupivacaine, because of its longer lasting effect (Cederholm 1994), less CNS toxicity and cardiotoxicity (Knudsen 1997), and vasoconstrictive properties (Kopacz 1989, Cederholm 1994). Also, ropivacaine is less chondrotoxic than bupivacaine in vitro (Grishko 2010), which is a theoretic advantage when glenoid cartilage is retained. A recent study also found ropivacaine less toxic than bupivacaine to rotator cuff tenofibroblasts in vitro (Sung 2014). The cytotoxic effect of local anesthetic is dependent on the duration of treatment, and this, combined with limited evidence of postoperative bolus injections providing significant analgesia, makes a single infiltration more appealing, especially when cartilage is retained. Blood ropivacaine levels have been found well below toxic levels using 400 mg in THA (Busch 2010). Epinephrine is a relevant adjuvant for prolonging the effect (Cederholm 1994), but due to the suspicion that it can cause blistering or skin necrosis, it may be best to avoid it in the solution used to infiltrate the skin (Toftdahl 2007). Ketorolac and other NSAIDs are not attractive as adjuvants in the solution to be injected, due to suspicion of NSAIDs affecting tendon-to-bone healing (Cohen 2006), and the necessity of a tenotomy and reinsertion of the subscapularis muscle in order to perform a shoulder replacement. Timing and duration may influence this effect on healing (Su 2013), but studies are thus far inadequate to conclude on the safety of infiltration into a tendon which is to be reinserted. In designing study I, LIA consisting of a single intra-operative infiltration of 300 mg ropivacaine with epinephrine (no epinephrine for the skin) was therefore chosen.

## **Dexamethasone**

Dexamethasone is a long-acting glucocorticoid often used to prevent postoperative nausea and vomiting (Holte 2002, Carlisle 2006, Karanicolas 2008). Dexamethasone also has an analgesic effect that lasts up to 24 hours, making it ideal for outpatient surgery (De Oliveira 2011, Waldron 2013). As dexamethasone is a glucocorticoid, the effect is mediated by nuclear receptors, making the time to effect quite long, and therefore it should be administered at least 1 hour preoperatively. It is often used as part of a multimodal, opioid-sparing analgesic regimen (Dahl 2014). The safety of perioperative single doses of glucocorticoids has been repeatedly reported in a large scale study (Dieleman 2012), review (Salerno 2006) and meta-analysis (Sauerland 2000): although, the methods used for detecting adverse effects may be insufficient in many of the clinical trials (Mathiesen 2014).

Two meta-analyses of the analgesic effect are based on studies of doses ranging from 1.25 to 80 mg dexamethasone, and include a wide variety of surgical patients (De Oliveira 2011, Waldron 2013). The analgesic effect is most likely mainly mediated by the anti-inflammatory effect, which inhibits peripheral sensitization (Salerno 2006) and the surgical stress response (Holte 2002). Therefore, the optimal dose is probably dependent on the extent of the surgery (the extent of the resulting inflammation), and thus the magnitude of effect found in the meta-analyses cannot be translated directly to different surgeries. Both meta-analyses show that there is a dose-response effect, but only De Oliveira et al. (De Oliveira 2011) included studies with doses above 20 mg, of which there were two. For shoulder surgery, dexamethasone has been studied as an adjuvant to prolong the effect of nerve blocks (reviewed in (Choi 2014)). However, a study with systemic (intravenous) dexamethasone compared to dexamethasone as an adjuvant in ISB revealed a similar effect (Desmet 2013).

The optimal dose of dexamethasone for minor shoulder surgery has not previously been examined, and improved analgesia could possibly be obtained by using a higher dose than the commonly used dose of 8 mg for prevention of nausea and vomiting. Although doses as high as 80 mg have been used perioperatively (Karst 2003, Aminmansour 2006), the maximal endogenous production of cortisol (225 mg/day) corresponds to approximately 8.5 mg/day dexamethasone (Mager 2003, Dorin 2012), and the highest possible dose of interest for minor arthroscopic surgery is estimated to be 40 mg.

## **Chronic postoperative pain**

In contrast to the acute postoperative pain described in the beginning of this section, chronic (or persistent) postsurgical pain continues beyond the healing period. Chronic postsurgical pain has been defined as pain developed after a surgical procedure, lasting at least 2 months (or beyond the usual healing period), not caused by anything other than surgery (e.g. continuing malignancy or chronic infection) and not attributable to a pre-existing problem (Macrae 1999). This definition has recently been proposed altered to: pain developed or intensified after surgery, lasting at least 3-6 months and significantly affecting quality of life, continuing from acute postsurgical pain or commencing after a pain-free period, localized to the surgical field or relevant innervation area, and other causes excluded (Werner 2014). Other causes are the classic surgical complications such as infection, medical device-related problems, remaining malignancy/osteoarthritis/instability and the like, and it may be reasonable to consider the complications remaining in the definition as painful nervous system sequelae in the widest sense. This pain can be nociceptive due to damaged tissue continuously activating nociceptors (chronic inflammation/scar tissue pressing on nerves), but can also, instead of a normally functioning nervous system responding to stimuli, be an injured nervous system causing (neuropathic) pain. In some cases, some of the severed afferent fibers do not heal, regenerate, or simply undergo apoptosis, but instead start to produce ectopic firing (firing not from the normal distal end of the axon, but from any other part such as a neuroma), a phenomenon commonly seen in phantom pain and stump pain. Also, complex regional pain syndrome may arise. As with nociceptive and inflammatory pain, neuropathic pain involves massive input to the central nervous system, causing central sensitization (Backonja 2001). The emotional and social consequences of chronic pain include fear, depression, guilt, and withdrawal. As persistent postsurgical pain is (by definition) iatrogenic, focus should be on minimizing this complication to surgery as much as possible (Carroll 2013).

For a wide variety of procedures, it is established that a subgroup of patients experience persistent postsurgical pain (Johansen 2012, Simanski 2014). The incidence is highly dependent on the extent and type of surgery. For hip replacement, incidence is estimated to be 12 % (Nikolajsen 2006) and for knee replacement to be 20 % (Baker 2007). In shoulder replacement no similar studies have been published previously, but in one review the prevalence of severe pain is estimated to be 9 % after 2-12 years in osteoarthritis patients. A review article focusing on failed shoulder replacement found the incidence of neurologic injury after the procedure to be 0.6 % to 4.3 % (Wiater 2014).

Persistent postoperative pain following shoulder replacement is not entirely unexpected, given the extent of surgery, the dislocation of the joint during the procedure resulting in traction on the nerves, and the use of interscalene brachial plexus block or catheter.

Risk factors of persistent pain have been investigated for other types of surgery. Logically, intraoperative nerve damage and the extent of surgery are important risk factors (Katz 2009). Other risk factors include genetic factors, age, psychosocial factors, type of anesthesia, pain elsewhere than the surgical site, other comorbidities, preoperative pain, and acute postoperative pain (Althaus 2012, VanDenKerkhof 2013). As persistent postsurgical pain has not previously been examined for shoulder replacement, a logical first step is a questionnaire study of a large cohort of shoulder replacement patients to establish prevalence, characteristics, and putative risk factors. As a limitation inherent in the use of a questionnaire, the underlying causes of pain cannot be validated, and so Macrae's definition of chronic postsurgical pain (Macrae 1999) cannot be applied. When prevalence, characteristics and risk factors have been examined, subgroups found to be at increased risk can then be the focus of studies aiming to prevent chronic pain or minimize its consequences.

## Objectives and hypotheses

The overall aim of this dissertation was to investigate the effectiveness of two new pain treatments and to study the epidemiology of persistent pain after shoulder replacement.

The specific objectives and hypotheses were as follows:

1. To compare the effectiveness of LIA and ISC after shoulder replacement, assessed by differences in postoperative opioid consumption and pain intensity.

Hypothesis: LIA is superior to ISC, resulting in lower opioid consumption and lower pain intensity in patients receiving LIA compared to patients receiving ISC.

2. To evaluate whether a high dose of dexamethasone (40 mg) could significantly improve analgesia compared to a commonly used dose of dexamethasone (8 mg) after discharge following ASD and/or ACR, assessed by differences in postoperative pain intensity and analgesic consumption.

Hypothesis: Dexamethasone 40 mg will decrease pain intensity and analgesic consumption compared to dexamethasone 8 mg and placebo.

3. To describe the prevalence of, the characteristics of, and risk factors for persistent shoulder pain 1-2 years after shoulder replacement performed in Denmark.

Hypothesis: The prevalence of pain experienced constantly or every day within the last month at a level that interferes much or very much with daily activities is approximately 9 %, with roughly half of these experiencing neuropathic pain characteristics. Age, sex, pain elsewhere than the shoulder, severity of preoperative pain, and severity of acute postoperative pain are risk factors.

## Methods

### Assessment of postoperative pain

The natural history of postoperative pain was first examined by counting the number of patients requiring intramuscular morphine injections (Loan 1967, Wallace 1975). This has been improved by quantifying the dispersion of intravenous morphine by patients themselves using patient-controlled analgesia, PCA (Bullingham 1984). This method is still not wholly reliable, since many factors other than pain intensity influence opioid intake. Pain measurement can be done by using a verbal rating scale (VRS: none, mild, moderate, or severe pain, or similar terms), a visual analog scale (VAS: a 10-cm line with ends labeled “no pain” and “worst imaginable pain” or similar terms where the patient marks a point on the line), or a numeric rating scale (NRS: verbal or written, the patient gives a number from 0 to 10 corresponding to their pain intensity, 10 being worst pain).

The VAS and other pain measurement instruments have been validated and compared, but discussion persists as to whether pain can be accurately and objectively measured, since validation of a subjective experience is problematic. Although many consider the VAS to be a ratio scale, this has been contradicted by some (Kersten 2012). Furthermore, calculating a mean pain in a group of patients and comparing this with the mean pain of another group of patients is probably oversimplifying the reality of the widely different patient experiences (Frey-Law 2013). For the studies of this dissertation, the NRS 0-10 was used, as it may be more understandable for patients than the VAS, and it is more sensitive than the VRS (Williamson 2005).

### Ethics

All three studies were conducted in accordance with the Declaration of Helsinki (World Medical Association 2013) as well as Danish law and recommendations from the National Committee on Health Research Ethics. Patients of all three studies were asked to fill out questionnaires and possibly participate in telephone interviews, but no further hospitalization or ambulatory visits were necessary. The studies were registered with <https://clinicaltrials.gov/>, and permissions were granted from the Danish Data Protection Agency. In the two clinical trials, patients were given experimental treatment after a thorough investigation of the available knowledge in the field, revealing both [1] no suspicions of the interventions being unsafe and [2] high likelihood of them being beneficial. The two clinical trials were approved by the Central Denmark Region Committee on Health Research Ethics before inclusion began, and written informed consent was obtained from all

participants. The protocols of the randomized studies allowed prompt administration of analgesics on request, both by staff during hospital stay and by instructed patients themselves after discharge. Possible harm was carefully monitored throughout the study period. In case of harm, participants were eligible for insurance payments from the Danish Patient Compensation Association, just as other patients receiving public healthcare services in Denmark. The novelty and importance of the studies were considered greater than the inconvenience and risk to the participants, and the results were accurately reported and published in (or submitted to) international medical journals without undue delay.

## **Study I: LIA vs. ISC for shoulder replacement**

### Study design:

This was a randomized controlled clinical trial, in which the control group received the “gold standard” of ISC for pain alleviation. As ISC often results in rather obvious numbness, paresthesia, and motor block, we found it impossible to conduct the trial in a blinded manner (involving sham catheters in the LIA group). The groups were provided the interventions in parallel, so any changes in practice over time would affect the two groups equally, and the random allocation was unpredictable to the involved staff. It was a pragmatic superiority trial in relatively unselected patients under flexible conditions (with many surgeons and anesthetists involved) to test the effectiveness of LIA for shoulder replacement in a clinical setting. Due to the expected rate of inclusion, it was necessary to involve two centers to achieve the required number of patients within a reasonable time.

### Randomization:

Randomization was done to avoid bias in group assignment (selection bias). The random allocation sequence was computer generated (<http://www.randomization.com>) using a 1:1 ratio and blocks of eight subjects within which the order of treatments was random. From the resulting list of numbers and treatments, allocation envelopes were numbered 1-96, each containing a slip of paper with the number and the allocated treatment. The envelopes were sealed and not translucent. The generation of the list and the preparation of allocation envelopes were done by an assistant not otherwise involved in the study. The list was kept locked away in a sealed envelope, and the allocation envelopes were kept by the operating theatres in Horsens (envelopes 1-40 and 81-96) and Aarhus (envelopes 41-80). Envelopes were opened sequentially by the anesthesiologist just prior to applying, or not applying, the ISC.

### Pilot patients:

Before the trial, four pilot patients received LIA (one in Horsens, three in Aarhus) for proof of concept and to refine the method. These four patients received 40 mg, 30 mg, 86 mg, and 10 mg oral morphine equivalents, respectively, during the first 24 hours after surgery.

### Patients:

Patients scheduled for primary shoulder replacement at either Aarhus University Hospital or Horsens Regional Hospital, Denmark, were consecutively screened for the possibility of being included. To improve homogeneity, the included patients had no severe chronic neuropathic pain or sensory disturbances in the shoulder, no recent shoulder fracture, were not to receive a reverse shoulder replacement, and were below 90 years of age. To allow randomization, patients had to undergo surgery in general anesthesia and not in regional anesthesia. For safety reasons, the included patients had no allergy to amid-type local anesthetics and were not pregnant. For legal and ethical reasons, the included patients were above 18 years, and were mentally able to provide informed consent.

### Enrolment:

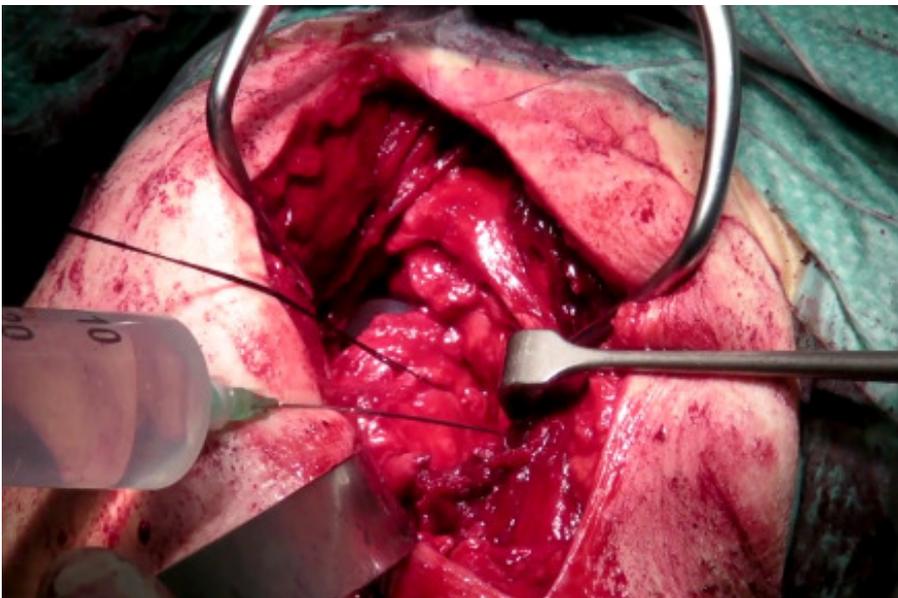
Patients fulfilling the criteria were informed of the possibility to participate in the study by the surgeon during the ambulatory visit during which the decision to operate was made. At the same time, written material describing the study was given to patients. Patients were contacted by telephone after a few days in order to answer any questions they may have had and to review the given information. If patients had not received the written information as planned, this was sent to them, and patients had at least 1 day to consider their participation before being called again. The patients were asked to provide a preliminary consent by phone to allow investigators to be present and prepared on the day of the operation, where the written informed consent was collected.

### Treatment:

For a detailed description of the standard protocol for anesthesia and the surgical technique, please see Paper I. The interventions of ISC and LIA are also meticulously described in the paper. Briefly, patients in the ISC group received an ultrasound-guided interscalene brachial plexus block using 7 ml ropivacaine 0.75 %, followed by infusion of 0.2 % ropivacaine 5 ml/hour using an elastomeric infusion pump with PCA, allowing patients to self-administer extra doses of 5 ml by pressing a button (Easypump with PCA, B. Braun Melsungen, Germany). The pump was disposed of by the instructed patient after 48 hours. Patients in the LIA group received infiltration with 150 ml ropivacaine 0.2 % during surgery (Figure 3). Epinephrine was added to the ropivacaine (except for

that infiltrated in the skin), and deposits were placed around the axillary nerve and suprascapular nerve, additionally the solution was infiltrated systematically in the operating field. The surgeons and anesthetists involved were thoroughly instructed in the techniques, orally and by written descriptions. Furthermore, the ISC technique was demonstrated on a patient with one of the involved anesthesiologists of each hospital present, and the LIA technique was video recorded on two of the early participating patients, and the most illustrative edited video was distributed electronically to participating surgeons. The nursing staff in the ambulatory clinics, surgical wards, operating theatres, and recovery rooms of both hospitals was instructed in the treatment of participating patients. After the trial commenced, the protocol was changed to allow for rescue interscalene brachial plexus block. This was done because 4 of the first 11 patients in the LIA group received more than 30 mg intravenous morphine in the postoperative care unit (PACU) as well as one patient in the ISC group, whom, having no effect of the catheter, received a new single-shot block at 2 a.m. on the night after the operation.

**Figure 3. Local infiltration analgesia being performed after cementing of the glenoid component and humeral stem of a total shoulder arthroplasty.**



Outcome measures:

The primary outcome measure was supplementary systemic opioid consumption during the first 24 hours postoperatively. Opioid was administered according to very specific guidelines for both the PACU and the ward, based on patients' pain scores (described in Paper I). Opioids were expressed

as oral morphine equivalents, converted by a factor of relative potency (McPherson 2009): Doses of intravenous morphine were multiplied by 3 (3:1 intravenous morphine), and similar calculations were made for other opioids: 300:1 intravenous fentanyl, 0.3:1 intravenous pethidine, 0.1:1 oral tramadol, 1.5:1 oral oxycodone and 3:1 intravenous nicomorphine. Secondary outcomes were pain scores at 0, 2, 4, 8, 24, 32, 48, 56, and 72 hours, nightly pain when worst, analgesic consumption and side effects for the first 3 days, and complications for the first 3 months postoperatively.

#### Data collection:

Patients were provided with a questionnaire in which to report their preoperative pain intensity and analgesic use, and their postoperative pain intensity, analgesic use, and side effects for the day of surgery and the following 3 days. The questionnaire was developed based on the chosen outcomes and on experience obtained from a similar previous study (Toftdahl 2007), as well as GCP data documentation practices (ICH 1996). The questionnaire was refined through qualitative pilot testing among research colleagues. The Danish patient questionnaire is appended to this dissertation.

Patients were introduced to the questionnaire by their nurse preoperatively, and filled it out independently or assisted by their nurse (until discharge). Data obtained from medical files were registered in a paper form and digitalized using Epidata version 3.1 (Epidata Association, Odense, Denmark) together with the questionnaire data. Final follow-up was after 3 months, at which time the patients were seen by the operating surgeon, and any complications registered in the medical files were noted. If for any reason patients were not seen after 3 months, they were contacted by telephone for final follow-up.

#### Statistics:

The required sample size was estimated using a formula specific to studies comparing two means, and rounded up to allow for drop-outs and non-normal distribution of the primary outcome. We aimed to find a difference in mean ( $\mu$ ) opioid consumption of 10 mg during the first 24 hours, and expected a standard deviation (SD,  $\delta$ ) of 15 mg. With  $\alpha = 0.05$  and  $\beta = 0.20$ , the sample size was calculated to be 35.55 participants, rounded up to 40 participants in each group.

$$n = \frac{2 * \delta^2 * f(\alpha, \beta)}{(\mu_1 - \mu_2)^2}$$

$$n = \frac{2 * 15^2 * 7.9}{10^2} = 35.55 \text{ patients}$$

Data were analyzed using Stata software version 12 (Statacorp, Texas, USA). Patients were excluded from analysis if the operation was cancelled, or if they did not receive the allocated intervention, withdrew consent, or had missing data for the primary outcome. Analysis was based on the available data without imputation of missing values.  $P < 0.05$  was considered statistically significant. Descriptive statistics used means (SD) for normally distributed data, medians (IQR) for non-normally distributed data, and counts (%) for categorical or dichotomous data. Statistical tests of association were Student's t-test for normally distributed data and Wilcoxon rank-sum (Mann-Whitney) test for non-normally distributed data. For categorical data, a chi-squared test was used, unless numbers were below 10 per field, in which case a Fisher's exact test was used.

## **Study II: Dexamethasone for ASD/ACR**

### Study design:

This was a blinded, randomized, placebo-controlled clinical trial, the groups being provided the treatment in parallel. It was a pragmatic superiority trial of the effective analgesic benefit of a higher dose of dexamethasone. It was monitored by the GCP Unit of Aarhus University Hospital. A placebo group was included to determine whether any analgesic benefit was present at all, in the event that no difference was found between the two groups receiving active treatment.

### Randomization and blinding:

Randomization was conducted by the hospital pharmacy, using a computer generated list and opaque envelopes as described for study I. The pharmacy serving Horsens Regional Hospital is located at Aarhus University Hospital. Randomization was restricted, using 1:1:1 ratio and blocks of 15 subjects within which the order of treatments was random, totaling 75 numbered treatment allocations (1-75). The list was kept concealed in the pharmacy. When preliminary oral consent was obtained and the date for surgery was known, the next number was ordered by fax from the pharmacy. The study drug was prepared and labeled according to good manufacturing practice and consisted of Fortecortin (dexamethasone 4 mg/ml in glass ampoules as dexamethasone dihydrogen phosphate-disodium) in 100 ml saline 0.9 % (Figure 4). The pharmaceutical company (Merck Serono, Darmstadt, Germany) was notified that the study was to take place, but was otherwise uninvolved in the study. The study drug was delivered by regular pharmacy transport or by taxi, as shelf life was first estimated to be 24 hours, later re-assessed to be 96 hours. If a patient was secondarily excluded or for any reason did not receive the treatment (delivery failure), the next patient's order was placed for the same randomization number, and the letter "A" was added, for example 9A, and possibly 9B and 9C as necessary.

**Figure 4. Label of the study drug, for randomization number 9, containing dexamethasone 8 mg, 40 mg, or placebo in 100 ml saline.**



Blinding was complete for all involved except the pharmacists; patients, staff, and data collectors were blinded. The bags of study drug and delivery notes were completely identical in appearance except for the randomization number, batch number, and expiry date and time (Figure 4).

Furthermore, the primary analysis was performed blind (after final follow-up), as the groups were labeled A, B, and C, and only the placebo group was revealed, allowing comparison of the active groups until the first analyses had been performed. The blinding was then fully broken.

#### Patients:

Outpatients scheduled for ASD and/or arthroscopic ACR at Horsens Regional Hospital were consecutively screened for the possibility of being included. In order to improve homogeneity in the study group, patients were excluded if they were to receive nerve block, other surgery at the same time as ASD and/or ACR, were above 90 years, received daily glucocorticoids or stronger opioids (not counting tramadol and codeine), or received any daily analgesics for reasons other than pain in the shoulder to be operated on. If more extensive surgery than planned was carried out (e.g. rotator cuff repair), the patient was excluded secondarily. Patients were excluded for safety reasons if they were allergic to dexamethasone, had glaucoma, untreated/undertreated hypertension, or diabetes. For legal and ethical reasons, patients below 18 were not included. Patients fulfilling criteria were

provided detailed written and oral information prior to them accepting or refusing participation. Enrolment was executed as described above for study I.

#### Treatment:

Patients were allocated to one of three groups: The high-dose group receiving 40 mg dexamethasone (D40), the positive control group receiving 8 mg dexamethasone (D8), and the placebo group (D0) receiving normal saline 0.9 %. The treatment was given intravenously before surgery, infused over approximately 10 minutes. For a detailed description of the standard protocol for anesthesia and surgery, please see Paper II. Postoperative pain treatment included intravenous fentanyl and oral acetaminophen, ibuprofen, and morphine/tramadol as described in Paper II. Nurses in the recovery room and the patients themselves were carefully instructed in the analgesic regime to be followed.

#### Outcome measures:

The primary outcome was patient-reported pain intensity 8 hours after surgery, measured by NRS 0-10. Secondary outcomes were pain intensity, analgesic consumption, and side effects for the first 3 days, as well as complications for 2 months. Opioids were converted to oral morphine equivalents as in study I.

#### Data collection:

A questionnaire was developed for patients to complete on the day of operation and the following 3 days. The questionnaire was pilot tested before the study among 16 patients meeting inclusion criteria, all receiving 8 mg dexamethasone orally. The questionnaire was refined according to this qualitative validation as well as through input from research peers and GCP guidelines. The Danish patient questionnaire is appended to this dissertation. Patients were introduced to the questionnaire by their nurse preoperatively, at which time the first questions concerning preoperative pain and analgesic use were answered. The same nurse assisted in filling out the postoperative pain scores until the patient was discharged. Data from medical files were transferred to a paper form and digitalized as in study I. Final follow-up was undertaken at the regular visit to a hospital physiotherapist 2 months after surgery, where any complications were noted. If patients for any reason were not seen at 2 months, they were contacted by telephone and questioned about complications.

#### Statistical analysis:

The sample size calculation was based on our aim to find a marked improvement of 2 points on the NRS (0-10) in the 40 mg group compared to the 8 mg group at 8 hours after surgery. Using the

same formula as in study **I**, with SD estimated to 2.3 using the data from the pre-trial validation of the questionnaire,  $\alpha = 0.05$  and  $\beta = 0.80$ , the sample size needed was 21 patients, rounded up to 25 patients in each group to allow for incomplete follow-up.

Statistical analysis was performed as described for study **I**, except when all three groups were compared, in which case Spearman's rank correlation coefficient was used. Patients were excluded from analyses if they underwent more extensive surgery than planned (the secondary exclusion criterion), did not receive the study drug, or failed to return the questionnaire.

### **Study III: Persistent pain after shoulder replacement**

#### Study design:

This was an observational study, a cohort study in which the prospectively recorded baseline data were retrieved from a register and the follow-up was by patient questionnaire. Although studies of persistent pain may use a follow-up as short as 2 months, the healing process for shoulder replacement is longer, and a follow-up of at least 1 year allowed patients to be well beyond the healing period. To keep the study group homogeneous, the longest follow-up was 2 years, as very little change was expected to occur in the interval between 1 and 2 years after surgery.

#### Patients:

The cohort comprised of patients available in the Danish Shoulder Arthroplasty Register (DSR) who had received their first and only shoulder replacement between April 2011 and April 2012. They had to be above 18 years of age (as the study focused on the adult population), and not re-operated in the shoulder since the replacement surgery, as this would interfere with assessments of persistent postsurgical pain. The registry contains data on 91-92 % of all patients receiving primary shoulder replacement in Denmark during the period studied.

#### Data collection:

Data extracted from the registry included age, sex, diagnosis, prosthesis, previous shoulder surgery, supplementary surgery, and 1-year postoperative patient-reported data (Western Ontario Osteoarthritis of the Shoulder Index and two supplementary questions). The development and pilot testing of the questionnaire are described in the paper (**III**). The questionnaire incorporated the DN4 (Douleur Neuropathique 4 questions), to assess neuropathic pain prevalence (Bouhassira 2005). An English translation of the Danish questionnaire is appended to the published paper (**III**) and to this dissertation. The outcome chosen to distinguish between the groups with/without persistent pain was *pain experienced constantly or every day at a level that interfered much or very much with*

*daily activities*, using questions 8 and 11: “During the last month, have you experienced pain in the shoulder with the prosthesis?” and “Overall, how much does the pain bother you in your everyday life?”. This definition of persistent postsurgical pain is different to the definitions by Macrae and Werner, due to the impossibility of ruling out other causes of pain when using a questionnaire. Other questionnaire data were questions to assess participant eligibility, pain treatment, pain characteristics, and possible predictors of persistent pain. The questionnaire was sent in May 2013 with a reminder in June, allowing a follow-up of 14-26 months. If responses for the main variables were missing or unclear, patients were contacted by telephone or e-mail if they had agreed to this and provided their contact information. Data from the returned postal questionnaires were digitalized by a research assistant with double entry of approximately 15 % of questionnaires using a detailed standard operating procedure.

Response bias was expected in the form of those with persistent pain being more inclined to respond, and those with severe disability being less inclined to respond. This was addressed in the cover letter, prompting patients to reply regardless of experiencing pain or not, and encouraging them to ask others, or contact us, for assistance in answering the questionnaire. Recall bias was expected for the questions referring to the period just before and after the operation. The questions therefore used a verbal rating scale instead of a numerical rating scale, and a shorter period of recall (1 week instead of 1 month).

#### Statistics:

Sample size was determined indirectly by the number of patients who met the inclusion criteria and were available in the register. Patients were excluded if their dataset was incomplete for the questions defining persistent pain or for the predictor variables: age, sex, diagnosis, prosthesis type, pain elsewhere, and severity of acute postoperative pain. Descriptive and basic associative statistical analyses were performed as in study I. The confidence intervals for prevalence were calculated as exact binomial 95 % CI (Clopper-Pearson). For assessment of predictive factors of persistent pain, a multivariate logistic regression model was used: after descriptive statistics and cross tabulations/graphics of the possible predictor variables, interaction/collinearity was assessed, a univariate logistic regression was done for each predictor variable independently, interaction terms were tried, and the multivariate logistic regression model was fitted. Our hypothesized predictors “preoperative pain intensity” and “preoperative pain duration” turned out to be problematic questions for those receiving their replacement due to a new fracture, so these variables were

replaced by diagnosis in the regression. Since diagnosis was a variable which interacted with other predictors, the multivariate model was stratified by diagnosis. Factors were included to correct for unknown confounders (age, sex, body mass index) or if they were clinically relevant and there were enough data to allow inclusion in analysis.

## Results

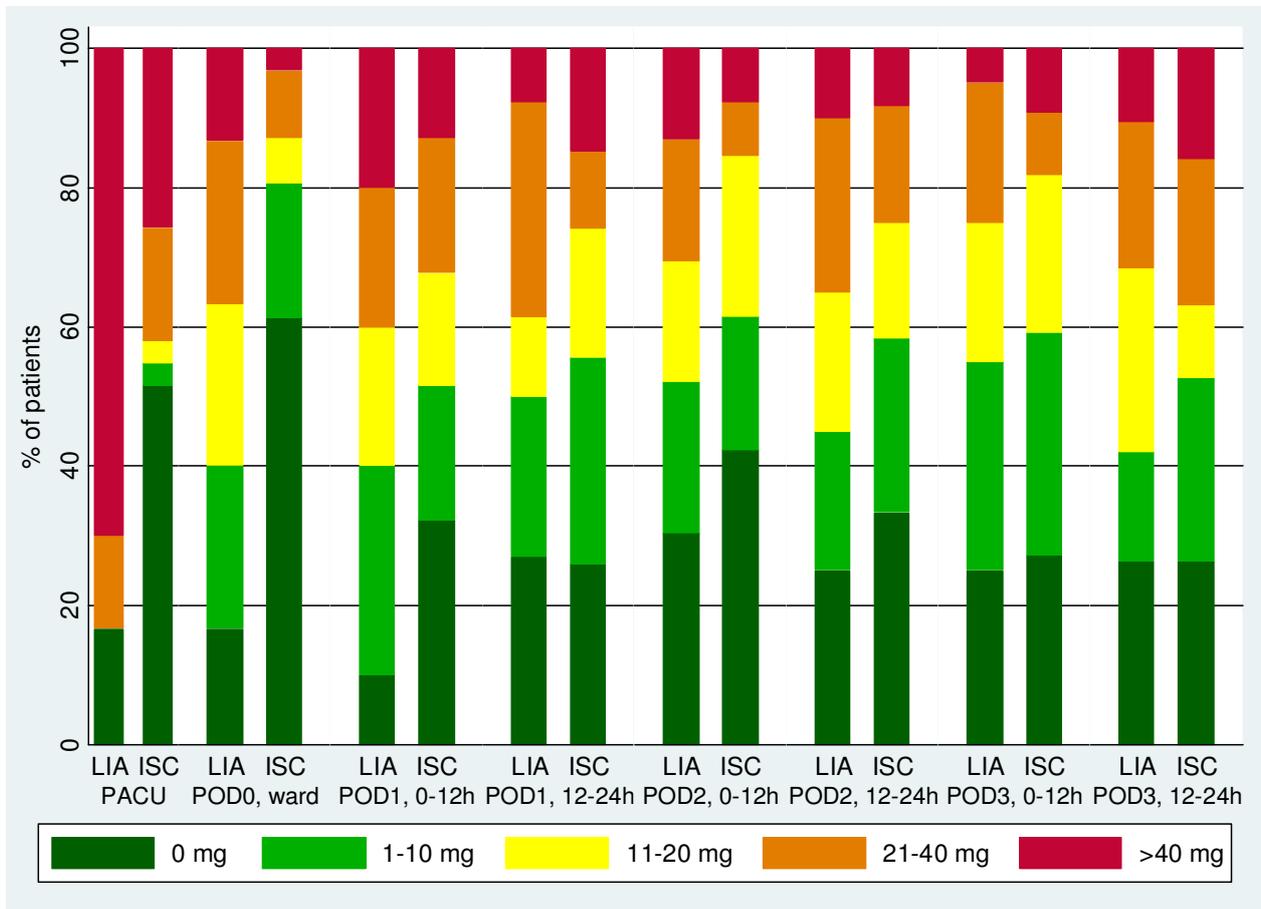
For a more in depth reporting of results, please refer to the respective papers (**I, II, III**).

### **Study I: LIA vs. ISC for shoulder replacement**

The study was terminated pre-schedule due to time constraints and evolvments in clinical practice over time (changes in staff and premedication). Of the 69 patients randomized, 61 patients were available for analysis of which 30 received LIA and 31 received ISC. The two groups were comparable with regard to baseline characteristics and reflected the target population well (Paper I). The majority of patients underwent surgery at Horsens Regional Hospital (39 patients versus 22 patients at Aarhus University Hospital).

Opioid consumption during the first 24 hours was markedly higher in the LIA group: median (IQR) 95 mg (70-150) in the LIA group compared to 40 mg (8-76) in the ISC group ( $p < 0.001$ ). This difference was present on the day of surgery, but was not seen on days 1 to 3 after surgery in the patients available for analysis. As a secondary outcome, opioid consumption for other time periods is illustrated in Figure 5 (not included in the paper). As depicted in the figure, 70 % of patients in the LIA group received more than 40 mg oral morphine equivalents in the PACU (21 patients, 9 from Aarhus and 12 from Horsens), compared to less than 30 % of patients in the ISC group (8 patients, all from Horsens).

**Figure 5. Opioid consumption over time, categorized according to use of oral morphine equivalents.**

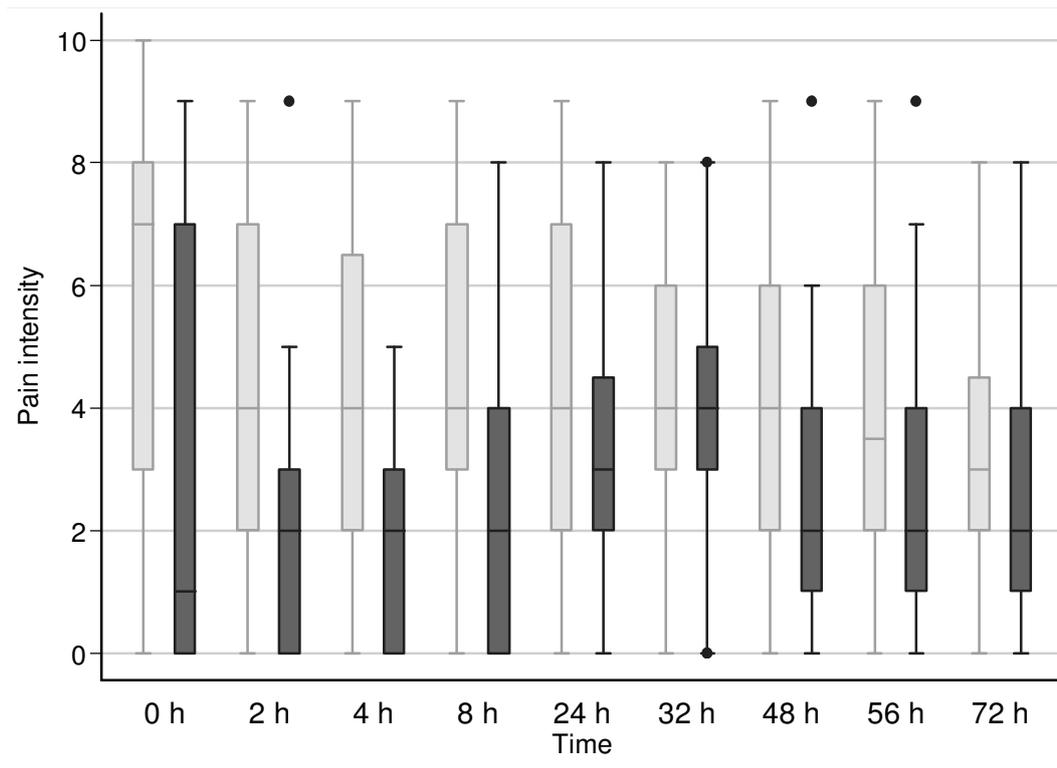


**PACU: postoperative care unit. POD: postoperative day. LIA: Local infiltration analgesia group. ISC: Interscalene brachial plexus catheter group.**

Similarly, pain scores were higher in the LIA group on the day of surgery (at 0, 2, 4, and 8 hours), but not significantly on days 1-3 (Figure 6). Pain scores in the ISC group were not consistently low during the 48-hour infusion as one would have expected.

Length of stay and side effects were similar between the two groups. Two complications occurred in the ISC group: one patient experienced prolonged severe dyspnoea, with pulmonary embolism diagnosed after 8 days and suspected phrenic nerve palsy lasting more than 3 months, and another patient had pinprick sensations in the forearm and thumb lasting 2 months.

**Figure 6. Postoperative pain intensity by numeric rating scale (NRS).**



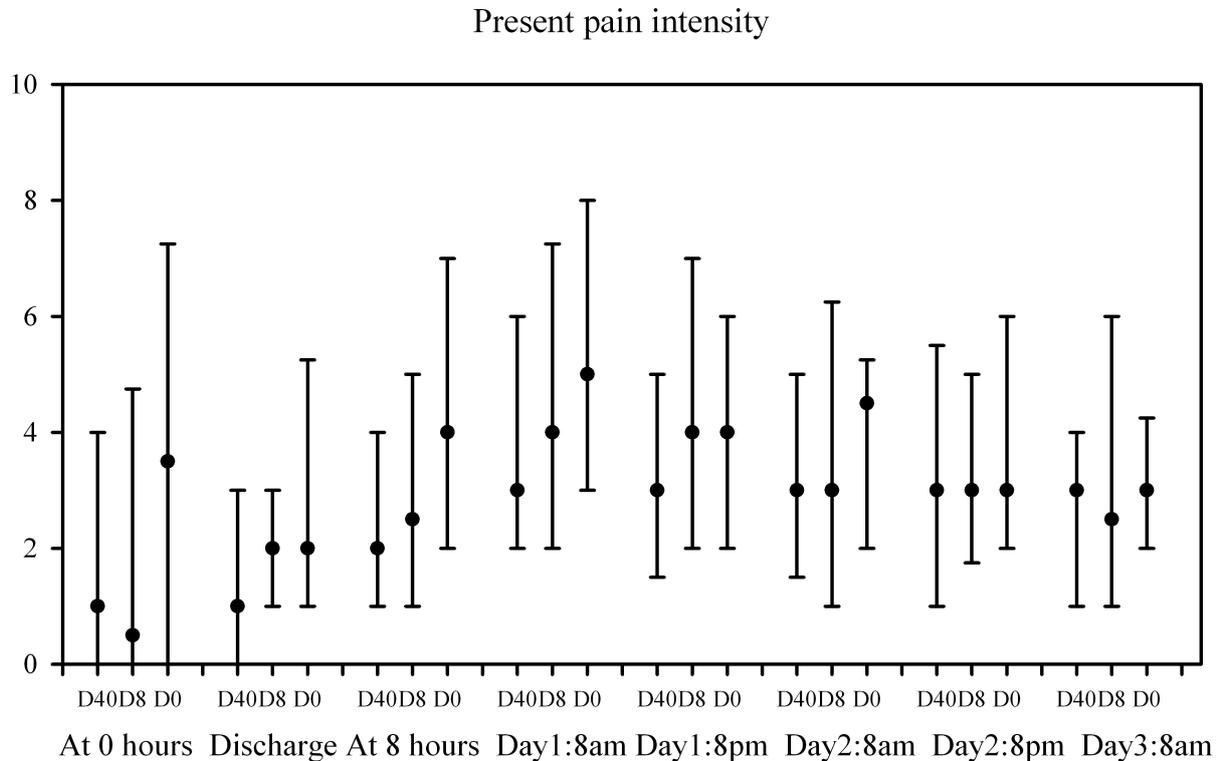
**Light grey: Local infiltration analgesia group. Dark grey: Interscalene brachial plexus catheter group.**

### **Study II: Dexamethasone for ASD/ACR**

Of the 101 patients randomized, 73 patients were available for analysis (D40: 25, D8: 26, D0: 22). Baseline characteristics were comparable between groups, except for bodyweight, which was greatest in the placebo group. A linear regression was made to assess whether this was a problem, but bodyweight did not affect the primary outcome of pain after 8 h.

Present pain intensity (Figure 7) was not significantly different between the active treatment groups at 8 h after surgery or at any other recording time. A dose-response relationship was found after 8 h and on the morning after the day of operation when all three groups were included in the analyses. Pain scores for D40 were significantly improved compared to D0 for these same time points, and for D8 compared to D0 regarding “pain when worst” after 8 h.

**Figure 7. Present pain intensity measured by numeric rating scale 0-10, as median and interquartile range.**



**D40: dexamethasone 40 mg group, D8: dexamethasone 8 mg group, D0: placebo group.**

Although pain intensity differed between groups as described, no significant differences in opioid or NSAID consumption were found. Side effects were also similar, although non-significant trends for a dose-dependent increase in stomach pain or discomfort and decreases in fatigue and bruising were seen. To assess whether blinding had been successful, patients were asked to guess their allocated treatment, and no association was found between the guesses and the actual treatment assignments.

### **Study III: Persistent pain after shoulder replacement**

Of the 786 patients registered in the DSR with one primary shoulder replacement, 538 patients were available for analysis (68 %). One hundred seventeen of the 538 patients had constant or daily persistent pain that interfered much or very much with daily activities (22 %, CI: 18-25).

Neuropathic pain characteristics as assessed by DN4-interview were reported by 66 of 505 patients (13 %, CI: 10-16). Whereas the prevalence of persistent pain was more frequent among fracture patients (29 %, CI: 23-35) than among osteoarthritis patients (16 %, CI: 11-21), the prevalence of neuropathic pain characteristics was independent of diagnosis. The analgesics consumed daily were

mainly acetaminophen (31 %) and opioids (19 %). Length of follow-up did not influence the prevalence of pain.

The multivariate logistic regression model (Table 1) was stratified by diagnosis of fracture and osteoarthritis, since this variable interacted with other predictors. There were too few patients with other diagnoses to model separate multivariate regressions for those groups. The effects of age, sex and BMI were small or non-existent, but they were kept in the model to correct for unknown confounders. Severe acute postoperative pain increased the odds ratio of having persistent pain regardless of diagnosis. Previous osteosynthesis and pain elsewhere predicted persistent pain in fracture patients, and a hemi-arthroplasty (compared to a total arthroplasty) predicted persistent pain in osteoarthritis patients.

**Table 1. Risk factors for persistent pain, 1-2 years after shoulder replacement.**

Variable	All patients, univariate	All patients, multivariate	Fracture, multivariate n=220	Osteoarthritis, multivariate n=222
Age	0.98 (0.96-1.00)	0.97 (0.95-0.99)	0.98 (0.95-1.01)	0.94 (0.90-0.99)
Female sex	1.2 (0.8-1.9)	1.3 (0.8-2.2)	1.3 (0.6-2.8)	2.2 (0.9-5.5)
BMI n=514	0.95 (0.91-0.99)	0.94 (0.90-0.99)	0.94 (0.88-1.01)	0.94 (0.87-1.01)
Severe pain first week	4.5 (2.9-6.9)	3.9 (2.4-6.2)	3.6 (1.9-7.0)	4.7 (2.1-10.8)
Pain elsewhere	1.9 (1.2-3.1)	2.0 (1.2-3.5)	2.9 (1.4-5.9)	1.2 (0.4-3.1)
Prev. osteosynthesis	4.3 (1.9-9.6)	4.0 (1.7-11)	3.4 (1.3-8.9)	none, not included
Suppl. cuff repair	1.9 (1.1-3.0)	1.6 (0.9-2.8)	1.2 (0.6-2.5)	2.3 (0.6-8.7)
Prosthesis type				
Hemi	1 (reference)	1 (reference)	too few,	1 (reference)
Total	0.18 (0.05-0.60)	0.19 (0.05-0.66)	not included	0.11 (0.02-0.70)
Resurfacing	0.57 (0.32-1.03)	0.60 (0.31-1.17)		0.52 (0.19-1.46)
Reverse	0.59 (0.35-1.00)	0.83 (0.45-1.50)		1.55 (0.46-5.15)

**Values are odds ratio (CI). BMI: Body mass index.**

## Discussion

This dissertation investigated the analgesic effectiveness of LIA for pain after shoulder replacement, as well as the effectiveness of high dose dexamethasone for pain after ASD/ACR. In addition, it investigated the epidemiology of persistent pain 1-2 years after shoulder replacement.

### Interpretation and comparison with the literature

In the first study, we found that the LIA group required more opioids and had higher pain scores than could be expected based on LIA studies in knee and hip replacements. To compare our results with other LIA studies, Table 2 illustrates the results of a Swedish study (Essving 2010), in which TKA patients underwent surgery under general anesthesia and the control group received saline, and the results of a THA study by Busch et al. (Busch 2010), where the majority of patients underwent surgery under general anesthesia, and the control group was not infiltrated with local anesthetics. These studies were blinded, used PCA (patient-controlled analgesia) with intravenous morphine, and had comparable control groups. As concluded in some reviews (Andersen 2014, Marques 2014), the effect of LIA may be somewhat less for THA than for TKA, and this is also implied in Table 2. Our results suggest that the effect in association with shoulder replacement surgery may be even less, although we did not compare the effect of LIA directly with placebo/intravenous PCA morphine.

**Table 2. Analgesic outcomes compared to other studies.**

	24-hour opioid consumption		Pain scores by NRS or VAS		Conclusion
	LIA	Placebo	LIA	Placebo	
Essving TKA	median 17 mg (range 1-74)	median 65 mg (range 36-131)	3 hours: median 1 (IQR 0-3)	3 hours: median 4.5 (IQR 2-6)	superior for 27 h
Busch THA	mean 29 mg (SD 19)	mean 43 mg (SD 25)	PACU: mean 3.5	PACU: mean 5.9	superior in PACU
Study I	median 32 mg (range 3-133) mean 39 (SD 28)		2 hours: median 4 (IQR 2-7), mean 5		inferior to ISC for 8 h

**Opioids are presented in intravenous morphine equivalents. LIA: Local infiltration analgesia. ISC: Interscalene brachial plexus catheter. NRS: Numeric rating scale. VAS: Visual analog**

scale. TKA: Total knee arthroplasty. THA: Total hip arthroplasty. PACU: Postoperative care unit.

**Essving P, Axelsson K, Kjellberg J, Wallgren O, Gupta A, Lundin A. Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty. Acta Orthop 2010 Jun;81(3):354-360.**

**Busch CA, Whitehouse MR, Shore BJ, MacDonald SJ, McCalden RW, Bourne RB. The efficacy of periarticular multimodal drug infiltration in total hip arthroplasty. Clin Orthop Relat Res 2010 Aug;468(8):2152-2159.**

To our knowledge, no studies have reported intravenous PCA opioid use after shoulder replacement without providing ISC or ISB as well. However, for open rotator cuff surgery, the mean consumption of intravenous PCA piritramide consumption has been reported to be 69.2 mg (SD 62.2 mg) over the first 72 hours (Hofmann-Kiefer 2008), corresponding to approximately 52 mg intravenous morphine. In comparison, our 72-hour collected opioid use (in intravenous morphine equivalents) in the LIA group was approximately mean 58 mg (SD 29), suggesting that the effect of LIA may be rather limited, even though the effect is established for use in knee replacements and, to a lesser degree, hip replacements.

This unexpected finding leads to the following hypotheses regarding possible explanations: It could be due to the tourniquet used in TKA minimizing early washout of ropivacaine, or because proper local cooling and compression are more easily attainable in the knee joint (Webb 1998, Andersen 2008). Also, the shoulder joint could be more difficult to infiltrate completely, as infiltration is in highly vascular and muscular tissue rather than connective tissue. In addition, pain may arise from traction to the brachial plexus, which is not infiltrated.

In the ISC group, more patients than expected needed considerable doses of opioids in the PACU, based on previously reported failure rates (Ahsan 2014). These patients all underwent surgery at Horsens Regional Hospital, where more anesthesiologists were involved than in Aarhus University Hospital, and these anesthesiologists each had a smaller case exposure. This supports the need for high expertise to ensure low failure rates for ISC. The rise in pain scores observed before the catheter was removed at 48 hours was most likely due to displacement of the catheter.

In the second study, the analgesic effect of dexamethasone was reaffirmed, although the benefit of increasing the dose from 8 mg to 40 mg was too small to be statistically and clinically significant. The effect size we found for 40 mg dexamethasone is comparable to other controlled studies using 9 or 10 mg dexamethasone in orthopedic surgery (Mattila 2010, Backes 2013). The same effect size, but of shorter duration, has been seen for ibuprofen: In an efficacy study involving various orthopedic patients, a single dose of 400 mg ibuprofen reduced VAS pain intensity scores by approximately 2 points compared to placebo (Heidrich 1985). In Cochrane reviews of acute pain medication efficacy, the outcome is not the numerical difference in VAS or NRS before and after the single dose, but instead the number of patients experiencing at least 50 % pain relief (where baseline pain is at least moderate). This number varies greatly, from 38 % to 75 % of patients after various surgeries, so a smaller response is common for all oral analgesic drugs (Moore 2011). The results of our study have provided evidence that the effect size of a very high dose of 40 mg dexamethasone is not significantly larger than could be expected from 8 mg, or than that of other studies using moderate doses.

After 1-2 years, 22 % of shoulder replacement patients experience daily pain that interferes much or very much with daily activities. This figure is not directly comparable to other studies, as the follow-up periods and the definitions vary. In a review of 40 shoulder replacement studies including mainly osteoarthritis patients, 9 % experienced severe pain after 2-12 years (van de Sande 2006). In hip replacements, 12 % experienced pain with at least moderate impact on daily life after 12-18 months (Nikolajsen 2006). These hip patients all had osteoarthritis, and the number should therefore be compared to the 16 % of osteoarthritis patients found in our study to have persistent pain. In knee replacements, 20 % of patients experienced pain rated 4 or 5 out of 5 after 14-23 months (Baker 2007).

The group of patients in our study experiencing neuropathic pain as assessed by DN4 interview was 13 % (66 of 505 patients). Of these 66 patients, 40 patients also met the criteria for persistent pain, whereas 26 did not. Symptoms such as numbness, tingling, and pins and needles may not be accompanied by substantial pain, and substantial postoperative pain is often not neuropathic (Remerand 2014). As our study illustrates the extent of the problem, clinical studies should be undertaken which can diagnose the causes of pain.

Patients at highest risk of persistent pain were fracture patients with pain elsewhere, previous (failed) osteosynthesis, and those who had severe acute postoperative pain during the first week after surgery. For osteoarthritis patients, risk factors were hemi-arthroplasty compared to total arthroplasty, and severe acute postoperative pain. The correlation between severe acute postoperative pain and persistent pain has been shown in many other studies (Macrae 2008). Revision surgery has been a reported risk factor in foot surgery (Remerand 2014), pain elsewhere has been found as a risk factor in hip replacement (Nikolajsen 2006), and the general outcome of shoulder replacement has been found to be better with total arthroplasty compared to hemi-arthroplasty (Bishop 2005, Radnay 2007, van den Bekerom 2013).

### **Methodological considerations and limitations**

To determine the effectiveness of the pain treatments, studies **I** and **II** were randomized clinical trials, and study **II** was also blinded and GCP monitored. Randomization should eliminate confounding, as groups should be comparable with regard to known and unknown possible confounders. In study **II**, bodyweight was higher in the placebo group, which necessitated a linear regression analysis to assess the possibility of bodyweight being a confounder; it was rendered unlikely. Obviously, it is impossible to make similar assessments for any unknown possible confounders.

The trials were pragmatic, using patients in hospital settings close to normal clinical practice, although patients were selected and their treatment, other than the intervention, was standardized to a large degree. We wished to evaluate the interventions in such a way that the results could be extrapolated to clinical practice. The “noise” from different nurses, surgeons, and anesthesiologists involved, as well as from protocol violations and any differing practices not taken into account in the protocol, may well have affected our results. Due to the randomization in blocks, any of these differences in clinical practice are likely to have affected the two groups equally, thereby not introducing bias, but only increasing the uncertainty of our estimates. This supports the validity of the conclusions based on the statistically significant results in the studies.

In most cases, statistical analyses showing insignificant differences between groups should not be interpreted as evidence of similarity between interventions, as the power is lower in the secondary analyses. In analysis of the primary outcome in study **II**, significance was not reached, but the power estimation from the sample size analysis was valid, as our estimation of SD held true. The

result of “no difference” is therefore credible, as our results render any true difference to be much smaller than 2 points on the NRS, and not likely clinically significant.

A limitation in both clinical studies involves opioid consumption – different opioids were converted to oral morphine equivalents according to equianalgesic doses (McPherson 2009). It is probable that the equianalgesic doses are inaccurate, and this could introduce bias if different types of morphine were used in the different groups. More intravenous morphine was used in the LIA group than in the ISC group in study **I**, and thus a bias could be introduced through the calculations. To overcome this issue, other studies have used intravenous PCA with an opioid as the only analgesic besides the interventions (and possibly acetaminophen and NSAID), making opioid use directly comparable. Our patients were discharged after a few hours (study **II**) or typically the day after surgery (study **I**), making intravenous PCA morphine more difficult and risky. Using intravenous PCA may have made it easier to assess the efficacy of the interventions, but may also have made it somewhat more difficult to determine their effectiveness in clinical practice. In study **I**, patients receiving ISC would have had two PCA devices, which may have confused patients and affected results. In study **II**, the expected use of morphine was rather low, and intravenous PCA morphine would have been excessive.

In study **I**, blinding was not possible. This may have introduced bias from patients and staff in assessing pain intensity and morphine requirements. In study **II**, the group receiving 8 mg dexamethasone had lower pain scores at 8 hours (NRS 2.5) than expected from the pilot study (NRS 5), which made any improvement offered by the high dose of 40 mg more difficult to establish. A possible explanation for the low pain scores could be that the study drug was given intravenously, whereas the pilot study included patients given 8 mg dexamethasone orally.

In study **III**, our selected cohort did not include all patients receiving a primary shoulder replacement in Denmark, as the DSR is only 91-92 % complete for the period studied (sampling bias). Selection bias is also a concern, as the original cohort of 786 patients was not fully available for follow-up. Among the 57 of the 223 patients who presumably met criteria and completed WOOS but were not available for our analysis, WOOS scores were worse than for those we included, suggesting that our estimate of persistent pain is not exaggerated. Still, the problem of

selection bias cannot be dismissed.

The questionnaire used in study **III** was piloted and assessed for content validity, but measurement bias (misunderstandings or not entirely pertinent questions) may still be an issue. DN4 has not been validated in Danish or in shoulder prosthesis patients; therefore, our estimate of neuropathic pain prevalence should be interpreted with reservation. Recall bias and present state bias were both expected for the questions concerning perioperative pain (the week before/after surgery), as well as their present state (during the last month). Their answers may also be affected by contamination bias (e.g. a headache at the time of filling out the questionnaire), pleasing bias (to please the involved surgeons after having received treatment), motivational bias (the treatment *should have* reduced their pain), or reporting bias (withholding relevant information for any reason). These limitations are inherent in the use of a questionnaire, and should be taken into account when interpreting the results.

## Conclusion and implications

The method of LIA provided inferior analgesia compared to ISC after primary shoulder replacement, and cannot be recommended as described here. The underlying reasons for the results are hypothesized to be a result of early wash-out of ropivacaine, poor cooling and compression, pain caused by traction to the brachial plexus, and anatomical challenges to the infiltration technique. These hypotheses should be tested, and could lead to optimization of the LIA technique in shoulder replacement or in other surgical procedures. Our study also contributes to the existing evidence that ISC can be problematic due to its complications and failure rates of the catheter infusion or the initial block, and it requires high expertise and case exposure to be reliable and to allow for safe, early discharge of patients.

Dexamethasone in a high dose of 40 mg did not improve analgesia compared to 8 mg in minor outpatient shoulder surgery when added to a multimodal analgesic regimen; although support was found for a dose-response relationship. Pain scores were low in the group who received 8 mg, but the effect of 40 mg dexamethasone compared to placebo was no greater than in other controlled studies using 9 mg or 10 mg dexamethasone. Even a very high dose of dexamethasone cannot obviate the need in some of these patients for opioid analgesics. Based on our results, the analgesic effect of 8 mg dexamethasone does not reach 2 points on the NRS (except for “worst pain” at 8 h), but future studies involving more patients may determine the dose at which the analgesic effect becomes clinically relevant. Use of dexamethasone is still attractive especially in outpatient surgery, as the effect is long-lasting (thereby not requiring of the patients that they self-administer the drug) and the side effects are minimal.

Persistent pain after shoulder replacement is a substantial daily burden to 22 % (CI: 18-25) of patients. As many as 13 % (CI: 10-16) of patients were screened positive for neuropathic pain. The analgesics consumed daily are mainly acetaminophen (31 %) and opioids (19 %). The causes of persistent pain and whether a closer follow-up could lead to improved pain treatment or treatment of underlying pathology should be investigated, given the high prevalence of pain found in this study. The risk factors found (fracture, previous osteosynthesis, pain elsewhere, severe acute postoperative pain, and hemi-arthroplasty) should also inspire the conduct of further studies of the etiology of persistent postsurgical pain, so preventive measures can be taken.

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## English summary

Postoperative pain after shoulder surgery is often considerable, and sufficient treatment is necessary to minimize suffering and improve rehabilitation. Postoperative pain usually subsides during the healing period, but some patients experience chronic pain which reduces their quality of life.

Our aim was to investigate [1] the effectiveness of local infiltration analgesia compared to interscalene brachial plexus catheter in shoulder replacement, [2] the analgesic benefit of a high dose of 40 mg dexamethasone compared to the usual 8 mg in minor arthroscopic shoulder surgery, and [3] the epidemiology of persistent pain 1-2 years after shoulder replacement.

In study **I**, 61 shoulder replacement patients were randomized to receive local infiltration analgesia or a brachial plexus catheter, and postoperatively reported their analgesic use, pain intensity, and side effects for 3 days, with final follow-up after 3 months for complications. The primary outcome was 24-hour opioid consumption, and our results showed that this outcome was poorest in the local infiltration analgesia group and that this also applied to pain scores on the day of surgery.

In study **II**, which was blinded and GCP-monitored, 73 shoulder arthroscopy patients were randomized to receive dexamethasone 40 mg, 8 mg, or placebo. Again, patients reported pain intensity, analgesic consumption, and side effects for 3 days, but in this case with final follow-up after 2 months for complications. There were no significant differences in pain scores or analgesic consumption between the 40 mg and 8 mg group. However, a dose-response relationship was confirmed when the placebo group was included in analysis.

In study **III**, 538 patients who had received a shoulder replacement in Denmark 1-2 years earlier answered a questionnaire describing their current pain, pain treatment, and possible risk factors. The prevalence of constant/daily pain which interfered much/very much with daily activities was 22 %; higher for fracture patients (29 %) than for osteoarthritis patients (16 %). Thirteen percent reported neuropathic pain characteristics. Risk factors for fracture patients were previous osteosynthesis, pain elsewhere, severe acute postoperative pain, and for osteoarthritis patients hemi-arthroplasty compared to total arthroplasty, and severe acute postoperative pain.

In conclusion, we present results showing poor effect of LIA for use in shoulder replacements, and the method cannot be recommended. We provide evidence that there is very limited analgesic benefit of increasing the dose of dexamethasone for use in shoulder arthroscopy, although the analgesic effect was reaffirmed. Finally, we provide data to support that persistent pain after shoulder replacement is a major problem, especially among fracture patients, and these results can serve to guide future investigations.

## Danish summary – Dansk resumé

Smerter efter kirurgi er ofte betydelige, og tilstrækkelig smertebehandling er nødvendig for at begrænse lidelse og forbedre rekonvalescens. For langt de fleste patienter forsvinder smerterne efterhånden som kroppen heler, men for nogle patienter opstår en kronisk smertetilstand, som mindsker livskvaliteten.

Formålet med denne afhandling var, at undersøge [1] effekten af lokal infiltrationsanalgesi i forhold til skalenerkateter ved skulderalloplastik, [2] den smertestillende effekt af en høj dosis på 40 mg dexamethason sammenlignet med de sædvanlige 8 mg ved mindre artroskopisk skulderkirurgi, og [3] epidemiologien for kroniske smerter 1-2 år efter skulderalloplastik.

I studie **I** blev 61 skulderalloplastikpatienter randomiseret til lokal infiltrationsanalgesi og skalenerkateter, og efterfølgende rapporterede de deres analgetikaforbrug, smerteintensitet og bivirkninger i 3 dage, med sidste opfølgning for komplikationer efter 3 måneder. Det primære effektmål var 24-timers opioidforbrug, hvor lokal infiltrationsanalgesi-gruppen havde ringere resultat, hvilket også gjaldt smertescores på operationsdagen.

I studie **II**, som var blindet og GCP-moniteret, blev 73 patienter randomiseret til dexamethason 40 mg, 8 mg eller placebo. Igen noterede patienterne smerteintensitet, analgetikaforbrug og bivirkninger i 3 dage, men her med sidste opfølgning for komplikationer efter 2 måneder. Der var ingen signifikante forskelle på smerteintensitet eller medicinforbrug mellem grupperne som fik 40 mg og 8 mg. Alligevel fandtes en dosis-respons sammenhæng når placebo gruppen blev medtaget i analysen.

I studie **III** besvarede 538 patienter, som 1-2 år tidligere havde fået en skulderalloplastik i Danmark, et spørgeskema vedrørende deres nuværende smerter, smertebehandling og mulige risikofaktorer. Prævalensen af konstante/daglige smerter som generede meget eller rigtig meget i dagligdagen var 22 % (CI: 18-25), højere for frakturpatienter end for artrosepatienter. 13 % (CI: 10-16) angav at have neuropatiske smertetræk. Risikofaktorer blandt frakturpatienter var: Tidligere osteosyntese, smerter andetsteds og svære akutte postoperative smerter, og for artrosepatienter: Svære akutte postoperative smerter og hemialloplastik frem for total alloplastik.

Sammenfattende præsenterer vi resultater, der viser ringe effekt af LIA for skulderalloplastik, og metoden kan ikke anbefales. Vi dokumenterer, at der er en yderst begrænset fordel ved at øge dosis af dexamethason ved skulderskopi, selvom den smertestillende virkning er bekræftet. Endelig fremlægger vi data som underbygger at kroniske smerter efter skulderalloplastik er et stort problem, især blandt patienter med frakturer, og disse resultater kan vejlede fremtidige undersøgelser.

## **Appendices:**

**Paper I**

**Paper II**

**Paper III**

**Questionnaire for Paper I:**

**“Spørgeskema i forbindelse med smertebehandling ved skulderprotese”**

**Questionnaire for Paper II:**

**“Spørgeskema i forbindelse med smertebehandling ved skulderoperation”**

**Questionnaire for Paper III:**

**“Questionnaire”**

**Theses from the Orthopedic Research Group of Aarhus University Hospital**

## Local infiltration analgesia versus continuous interscalene brachial plexus block for shoulder replacement pain: A randomized clinical trial

*Running title:* Local infiltration analgesia in shoulder replacement

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**Trial registry:** <http://clinicaltrials.gov/> identifier: NCT01362075

**Ethics approval:** Approved by the Central Denmark Region Committee on Health Research Ethics (May 9 2011, M-20110084).

**Conflicts of interest:** None.

**Sources of support:** The Health Research Fund of Central Denmark Region; The Family Hede Nielsen Foundation; the Danish Rheumatism Association; and the Augustinus Foundation.

The authors, their immediate families, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

**Acknowledgements:** We wish to thank all involved staff at Horsens Regional Hospital and Aarhus University Hospital, the project nurses providing assistance with inclusion and data collection during the maternity leave of KTB, Lise Viskum Hansen for help with data analyses, and Gerhardt Teichert and secretary Line Jensen for comments to the manuscript.

**ABSTRACT**

**Background:** Shoulder replacement involves significant postoperative pain, which is often managed by continuous interscalene brachial plexus block. Catheter displacement and complications limit the beneficial effect of the block. Local infiltration analgesia (LIA) has provided good results in knee replacement. We aimed to assess the effectiveness of LIA for pain after shoulder replacement.

**Methods:** Patients scheduled for primary shoulder replacement under general anesthesia were randomized to receive either LIA: local infiltration analgesia (150 ml ropivacaine 0.2% with epinephrine intra-operatively) or ISC: interscalene brachial plexus catheter (ropivacaine 0.75%, 7 ml bolus followed by 48-hour 5 ml/h infusion). The primary outcome was opioid consumption during the first 24 postoperative hours. Secondary outcomes were pain ratings, supplementary analgesics, and side effects for three days, and complications until 3 months after surgery.

**Results:** Data were analyzed for 61 patients (LIA: 30, ISC: 31). Twenty-four-hour opioid consumption was higher in the LIA group compared with the ISC group: median (IQR) 95 mg (70-150 mg) versus 40 mg (8-76 mg) ( $P = 0.0001$ ). No significant difference in opioid consumption was found between groups during the following three days. The LIA group had higher pain scores at 0, 2, 4, and 8 hours. Two patients in the ISC group had long-lasting complications.

**Conclusion:** The LIA technique cannot be recommended for shoulder replacement unless substantially modified. Occurrence of inadequate analgesia and complications following interscalene brachial plexus block prompt further studies into pain management after shoulder replacement.

**Level of evidence: Level I, Treatment study. Keywords:** Shoulder arthroplasty, local infiltration analgesia, interscalene brachial plexus block, postoperative pain.

## Introduction

Postoperative pain management affects the speed of recovery and the outcome of surgery, as adequate pain relief reduces complications and permits sleep, eating, and physiotherapy.<sup>12,19</sup>

Postoperative pain after shoulder replacement is often severe, and the recommended treatment is a preoperative interscalene brachial plexus block, followed by a postoperative continuous infusion of local anesthetic via an interscalene catheter (ISC).<sup>8,15,31</sup> The primary interscalene brachial plexus block can be effective in 98 % of cases<sup>9</sup> and provide almost complete analgesia lasting throughout the day of surgery.<sup>22</sup> However, the catheter placement is more technically challenging,<sup>15</sup> entails a risk of primary or secondary displacement<sup>9</sup> or pump failure,<sup>18</sup> and may provide less complete analgesia.<sup>22</sup> Side effects include hoarseness, dyspnea, and paresthesia,<sup>15</sup> but serious complications are rare.<sup>21,22</sup> Often patients are discharged before removal of the catheter, so the transition to oral analgesics takes place at home.

During the last 10-15 years, high-volume local infiltration analgesia (LIA) has been introduced for postoperative pain management after hip and knee replacement.<sup>3,20,33</sup> Several reviews have confirmed an analgesic effect comparable to epidural or femoral nerve block, especially for knee replacement.<sup>5,23</sup> During the operation, all affected tissues are infiltrated with a mixture of ropivacaine, ketorolac, and epinephrine. There are currently no results of LIA applied to alleviate pain after shoulder replacement, although other techniques involving subcutaneous, subacromial or intraarticular injections or infusions have been used in shoulder surgery with varying results.<sup>6,16,17,27</sup> Our aim was to compare the effectiveness of LIA and ISC after shoulder replacement, assessed by differences in postoperative analgesic use and pain scores.

## Materials and Methods

### *Patients and design*

This prospective, parallel randomized open-label clinical trial was conducted at Aarhus University Hospital and Horsens Regional Hospital, Denmark. The study was approved by the Central Denmark Region Committee on Health Research Ethics (May 9 2011, M-20110084) and the Danish Data Protection Agency. It was registered at <http://clinicaltrials.gov/> with identifier NCT01362075. Patients scheduled for primary shoulder replacement were screened for eligibility. Exclusion criteria were severe chronic neuropathic pain or sensory disturbances in the shoulder, recent shoulder fracture, reverse prosthesis shoulder replacement, operation performed without general anesthesia, allergy to amid-type local anesthetics, age below 18 or above 90 years, pregnancy, and lack of mental ability to provide informed consent. All patients provided written informed consent prior to participating, and were enrolled by their operating surgeon or the first author. Patients were allocated to treatment groups based on a computer generated random allocation sequence

(<http://www.randomization.com>), using a 1:1 ratio and blocks of eight within which the order of treatments were random. The allocation sequence was transferred to an equivalent number of consecutively numbered, opaque, sealed envelopes, and the procedure was performed by an independent assistant. Upon study inclusion, each patient received the treatment assigned in the next numbered envelope, which was opened by the anesthesiologist just before surgery. Group ISC (interscalene brachial plexus catheter) received an interscalene brachial plexus block followed by continuous infusion of local anesthetic, and group LIA (local infiltration analgesia) received intraoperative local infiltration of the same local anesthetic with added epinephrine. It was not considered possible to perform the study blinded (with sham catheters in the LIA group), as numbness, motor block, and paresthesia in patients with interscalene brachial plexus block would be too obvious.

#### *Standard protocol for anesthesia and surgery*

All operations were performed using a deltopectoral approach with subscapularis tenotomy and reinsertion under general (total intravenous) anesthesia. Prophylactic antibiotics were administered before and after surgery, and antiemetics and laxatives were given as needed postoperatively. Both treatment groups received supplemental analgesics, provided by their attending nurse: In the postoperative care unit (PACU), i.v. morphine 0.1 mg/kg (0.05 mg/kg if age above 65 years) was offered to patients with pain scores of 3 or above (numeric rating scale, NRS 0-10; 0 = no pain and 10 = worst pain imaginable). If the pain score after 15 minutes remained at 3 or above, half of the primary morphine dose was offered every 10 minutes until the pain score was below 3. Discharge from PACU was made according to standardized criteria assessing sedation, respiration, oxygenation, blood pressure, heart rate, pain, nausea, mobility, and temperature. In the hospital ward, i.v. morphine 0.1 mg/kg (0.05 mg/kg if age above 65 years) was offered for pain scores of 5 or above, while patients with pain scores of 3-4 were offered oral morphine 10 mg (5 mg if age above 65 years) repeatedly every hour until the pain score was below 3. If opioid consumption within a 2 hour period reached the equivalent of 30 mg i.v. morphine, without pain scores falling below 3, a rescue interscalene brachial plexus block was offered as a single shot, regardless of randomization group. Patients who had received more than 40 mg of morphine within the first 24 hours, and still required opioids, received slow-release morphine prescribed around-the-clock. Acetaminophen 1 g, four times daily and ibuprofen 600 mg, three times daily was commenced after surgery unless contraindicated. Patients had the affected arm immobilized postoperatively in a sling day and night, making passive exercises for 6 weeks, after which the active rehabilitation started. Discharge criteria from the ward included sufficient pain management, ability to apply the sling correctly, and sufficient help in the home.

### *Regional techniques*

Group ISC received an ultrasound-guided interscalene brachial plexus block just before surgery, using sterile technique. The patient was placed supine with the head rotated 45 degrees contralaterally. The needle insertion point was at the lateral edge of the sternocleidomastoid muscle at the level of the cricoid cartilage. The skin was infiltrated with 2 ml of lidocaine 1 %. Ultrasound (SonoSite S-Nerve, SonoSite Inc., Bothell, WA, USA) was applied to obtain a cross section image of the subclavian artery with surrounding brachial plexus, and anterior ventral rami from C5 and C6 were identified between the anterior and middle scalene muscles. The 18 gauge needle (Contiplex S Ultra 18G x 2", B. Braun Melsungen AG, Melsungen, Germany) was advanced from the posterior end of the probe with in-plane technique, avoiding the external jugular vein and lateral to the sternocleidomastoid muscle to reduce the risk of secondary catheter displacement. Using 0.9 % (normal) saline dissection, the 20 gauge catheter was introduced 3 cm past the tip of the introducing needle and adjusted until saline injected via the catheter was observed by ultrasound to spread perineurally. After negative aspiration, 7 ml of ropivacaine 0.75 % was injected slowly via the catheter with intermittent aspiration. The catheter was fixed with tissue adhesive and a transparent dressing (Liquiband Standard Topical Skin Adhesive, Advanced Medical Solutions, Plymouth Ltd., Plymouth, United Kingdom) or a catheter securement device (Lock-It Plus, Smiths Medical, Rockland, MA, USA). After 3 to 6 hours, infusion of ropivacaine 0.2%, 5 ml/h was started, using a pump with patient-controlled 5 ml bolus function (Easypump C-bloc RA with PCA, B. Braun Melsungen AG, Melsungen, Germany). The catheter and pump were discarded by the instructed patient after 48 hours.

Group LIA received extensive infiltration of the surgical site with 150 ml ropivacaine 0.2% in three 50 ml syringes, of which the first two contained 0.25 mg epinephrine each. Infiltration was performed systematically and meticulously in all affected tissues accessible within 2.5 cm from the surface of the surgical site, with aspiration prior to injection, which was done during retraction of the needle. After preparing the joint surfaces and (when applicable) cementing the humeral stem and the glenoid surface, but before introducing the humeral articular surface, the first two 50 ml syringes of ropivacaine 0.2% with epinephrine were used. The first 15 ml of the first syringe were infiltrated around the axillary nerve, and the remaining volume was infiltrated around the glenoid cavity, the medial parts of the rotator cuff, and the posterior part of the joint capsule and surrounding tissues. The first 15 ml of the second syringe were infiltrated blindly through the skin to block the suprascapular nerve in the suprascapular notch. The remainder was infiltrated in tissues surrounding the exposed part of the humerus, including muscles and capsule of the anterior part of the joint, in order to cover the nociceptors of all soft tissues affected by surgery. After fitting the humeral articular surface and reinserting the subscapular muscle tendon, the 50 ml of the last

syringe without epinephrine (due to risk of skin necrosis) were infiltrated in the subscapular muscle and most anterior tissues of the operative site, including the subcutaneous tissues. Ice packs were applied to the shoulder as soon as possible after the wound was dressed.

#### *Data collection*

Patient characteristics, surgical data, and medication during the hospital stay were collected from medical files. The patients completed a questionnaire throughout the first three days regarding pain and analgesic medication before surgery, and postoperative pain after 0, 2, 4, 8, 24, 32, 48, 56, and 72 hours, worst pain at night, consumption of analgesics, and adverse effects. Patient data in the medical files and observational charts were scrutinized for possible adverse effects and complications until 3 months after surgery, when patients were followed-up by the surgeon. If the follow-up visit was made earlier or later, information about adverse effects and complications were collected by telephone interview after 3 months. The primary outcome was opioid consumption within the first 24 hours postoperatively, and secondary outcomes included pain scores, analgesic consumption, and adverse effects for the first 3 postoperative days, and complications up until the final follow-up at 3 months. Opioids were converted to oral morphine equivalents according to relative potency<sup>24</sup> [(all in mg, oral morphine:other): 3:1 i.v. morphine; 300:1 i.v. fentanyl; 0.3:1 i.v. pethidine; 0.1:1 oral tramadol; 1.5:1 oral oxycodone; and 3:1 i.v. nicomorphine].

#### *Statistics*

The target sample size was calculated to detect a difference of 10 mg in mean collected morphine consumption the first 24 hours. We expected a standard deviation of 15 mg and chose  $\alpha = 0.05$  and  $\beta = 0.2$ . The estimated required number of patients in each group was 36, assuming normal distribution. To allow for incomplete data collection and non-normal distribution, we decided to include 40 patients in each group.

The statistical analysis was performed using Stata software version 12 (StataCorp, College Station, Texas, USA). Data were analyzed for all who received the allocated treatment and underwent surgery, regardless of adherence to protocol as recommended by CONSORT<sup>25</sup>. Analyses of pain scores, analgesic consumption, and length of stay were made using two-sample Wilcoxon rank-sum (Mann-Whitney) test. For testing association of pain scores above 5 and hospital, a Fischer's exact test was used.  $P < 0.05$  was considered statistically significant.

## **Results**

Patients were included from July 2011. As the actual recruitment rate was much lower than the expected 75 patients yearly, the protocol and formal permissions were extended. Due to time constraints and evolvments in clinical practice (changes in staff and premedication), the study was terminated pre-schedule in July 2014, after 3 years of recruitment. 69 patients were included in the

study. Participant flow is depicted in the flow diagram (Figure 1). Four patients did not receive the allocated intervention; the surgical procedure was changed for three patients (arthrolysis, osteotomy, and rotator cuff repair), and in one case the LIA was not performed due to an oversight. Another patient in the LIA group withdrew consent after returning to the ward. One patient, who received interscalene brachial plexus block, experienced chest pain, coughing, and palsy of the recurrent laryngeal nerve, and the planned surgical procedure was cancelled. The demographic, analgesic, and surgical characteristics of the 61 remaining patients are presented in Table I.

### *Opioid consumption*

The primary outcome of opioid consumption during the first 24 postoperative hours was median (IQR) 95 mg (70-150) in the LIA group compared with 40 mg (8-76) in the ISC group ( $P = 0.0001$ ). The difference between groups was largest during the stay in PACU, and was also present for the remainder of the day of surgery (Table II). No differences between groups were found the first, second or third day after the day of operation.

### *Pain scores*

Pain scores were statistically higher in the LIA group at 0, 2, 4, and 8 hours (Figure 2,  $P < 0.01$  for each time point). No statistically significant differences were found for the subsequent pain measurements. Seven out of 27 patients in the ISC group had pain scores above 5 on awakening from anesthesia, suggesting unsuccessful nerve block, and these patients were all operated at Horsens Regional Hospital. Pain scores above 5 in the ISC group after discharge from the PACU and during ISC infusion (the first 48 hours), or in the LIA group, were not associated with the operating hospital. One patient in the LIA group received a rescue interscalene brachial plexus block due to break-through pain.

### *Other outcomes*

Length of stay in the PACU was median 2 h 55 min (range 37 min to 11 h) in the LIA group and 2 h 50 min (range 35 min to 7 h) in the ISC group ( $P = 0.29$ ). One patient in the LIA group, with known preoperative antihypertensive treatment and renal insufficiency, stayed 11 hours in the PACU due to hypotension and low urinary flow. Length of stay in hospital was median 2 days (range 1-3) in the LIA group and median 2 days (range 1-6) in the ISC group ( $P = 0.57$ ). Adverse effects questioned directly did not differ statistically between the two groups and comprised: Nausea, vomiting, fatigue, constipation, abdominal pain, hoarseness, dyspnea, ptosis, muscle weakness of the affected arm, pins-and-needles sensation, and wound leakage. Other adverse effects with possible relation to analgesia ( $n = 1$  unless otherwise stated) included in the LIA group: dizziness ( $n = 2$ ), hematoma, and drowsiness, and in the ISC group: sweating, reddening of skin on the shoulder, stinging in the axilla, pain in axilla and thorax side, slow healing ( $n = 2$ ),

and skin necrosis requiring re-suture. Two patients in the ISC group experienced longer lasting complications: One patient had prolonged severe dyspnea, and was diagnosed with pulmonary embolism after 8 days and suspected of phrenic nerve palsy lasting beyond the three months of follow-up. Another patient experienced pin prick sensation in the forearm and thumb lasting 2 months.

Protocol violations occurred in both groups, without exclusion of the patients. In one patient in the LIA group, the surgeon forgot to infiltrate the last 50 ml ropivacaine in the superficial tissues. In the ISC group, one catheter placement was unsuccessful and was aborted, one catheter was inserted after surgery while the block was performed before surgery, one rescue interscalene brachial plexus block was given due to break-through pain but without prior use of opioids as per protocol, two catheters were accidentally discontinued before 48 hours, one catheter was accidentally continued for 72 hours, two catheters were removed before 48 hours due to lack of effect, and on three occasions pumps without PCA were used.

## **Discussion**

The quality of analgesia in the LIA group was inferior to the ISC group, both with regard to consumption of opioids and pain scores. The poor analgesia in the LIA group, especially during the first 8 hours, is in contrast to the positive results seen with LIA for analgesia after knee replacement. Hypotheses for the difference could be that (1) the use of a tourniquet in knee replacement prevents early washout of ropivacaine, in contrast to the highly vascularized tissues in the shoulder, (2) shoulder pain may arise as a result of traction to the brachial plexus during surgery (and the plexus is not infiltrated), and (3) the knee is more easily accessible for cooling and compression, both of which could contribute to keeping the infiltrated ropivacaine localized and have been established as having an analgesic effect.<sup>4,28,29</sup> The difference cannot be explained by spinal anesthesia being used in knee replacements, since the analgesic effect only lasts a few hours, certainly not up to 8 hours, and LIA studies in knee and hip replacements using general anesthesia also have superior results.<sup>10,14</sup> It could be relevant to undertake studies of the pharmacokinetic profile<sup>7</sup> and distribution of infiltrate<sup>26</sup> as has been done in knees, to assess the suitability of the LIA technique for the shoulder joint. Supplemental intraarticular injections could have been performed to prolong the effect, but reports of chondrotoxicity<sup>11</sup> limited this option for resurfacing and hemi prosthesis, and toxicity of local anesthetics to tenofibroblasts has later been established in vitro.<sup>32</sup> Ketorolac could have been added to the infiltration solution, as studies have shown this to be beneficial,<sup>2,30</sup> but reports of NSAIDs impairing tendon-to-bone healing (in animal studies<sup>13</sup>) limited this option, as our surgical access involved reinsertion of the subscapularis tendon.

We had also expected better results for the ISC group; however, we found a high failure rate compared to the literature.<sup>1</sup> This may be due to many anesthesiologists involved at Horsens Regional Hospital, since the technique is known to require a high level of training and experience, and our practice has since changed to accommodate this to a greater extent. Since some patients reported pain scores above 5 at some point during ISC infusion, the catheter may have been displaced in these cases. This study is not dimensioned to assess the frequency of complications. The two longer lasting complications reported here have also been reported previously.<sup>21</sup> Some limitations of the present study should be considered. Firstly, the study was not blinded, and bias from patients and nurses may have occurred which could influence all outcomes. Secondly, due to the study being terminated before 40 participants were included in each group, the study may be underpowered. As our assumptions in the sample size calculations were proved wrong, the number of patients still provided statistically and clinically significant results for the primary outcome and for pain scores on the day of operation, but the insignificant results in other analyses cannot be interpreted as the two treatments being equivalent. Thirdly, opioid consumption was calculated on the basis of the different types of opioids, and the analysis of analgesic consumption would have been more accurate if only one type of opioid had been included, thereby avoiding possible errors in the conversion. We could have chosen to use patient-controlled analgesia (PCA) with intravenous morphine, but our patients were for the most part discharged the day after surgery, in some cases before 24 hours had passed, and we decided against ambulatory use of IV morphine (or prolonging hospital stay), and two PCA devices in the ISC group. Finally, the two methods of analgesia were very meticulously described, but as 8 anesthesiologists and 9 surgeons were involved, the treatment may not have been uniform. However, despite the noise being introduced into the statistical analysis by the many people on staff involved and the protocol violations, we still observed significant differences between the two groups.

## **Conclusions**

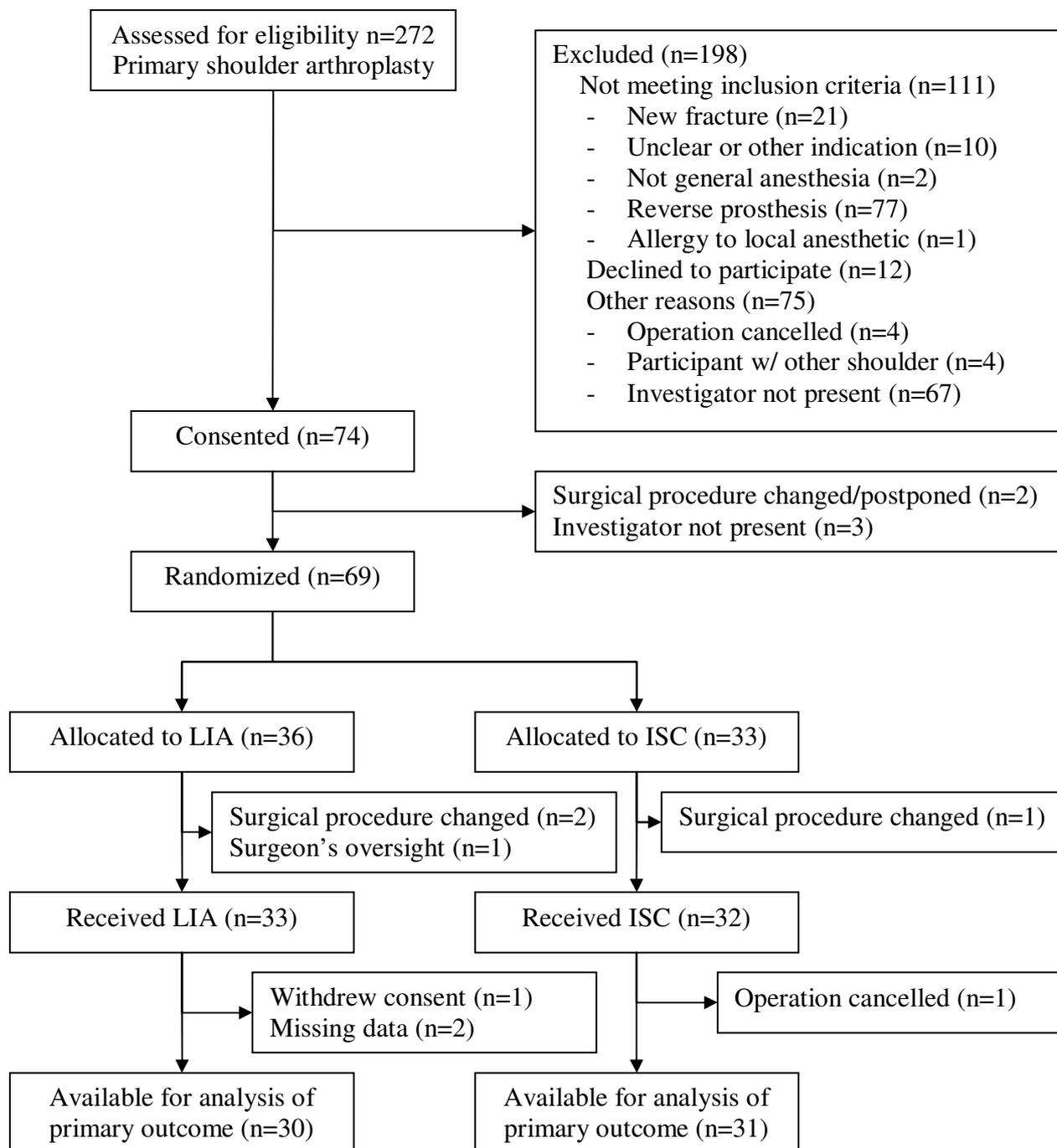
In conclusion, LIA provided inferior analgesia compared to ISC, but in both groups pain scores were higher than expected. Future studies should pursue solutions to the significant, unsolved problem of intense pain following shoulder replacement without the contingent risk of long-lasting complications.

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**Figure 1** Flow diagram.

LIA: Local infiltration analgesia. ISC: Interscalene brachial plexus catheter.

**Table I** Patient characteristics.

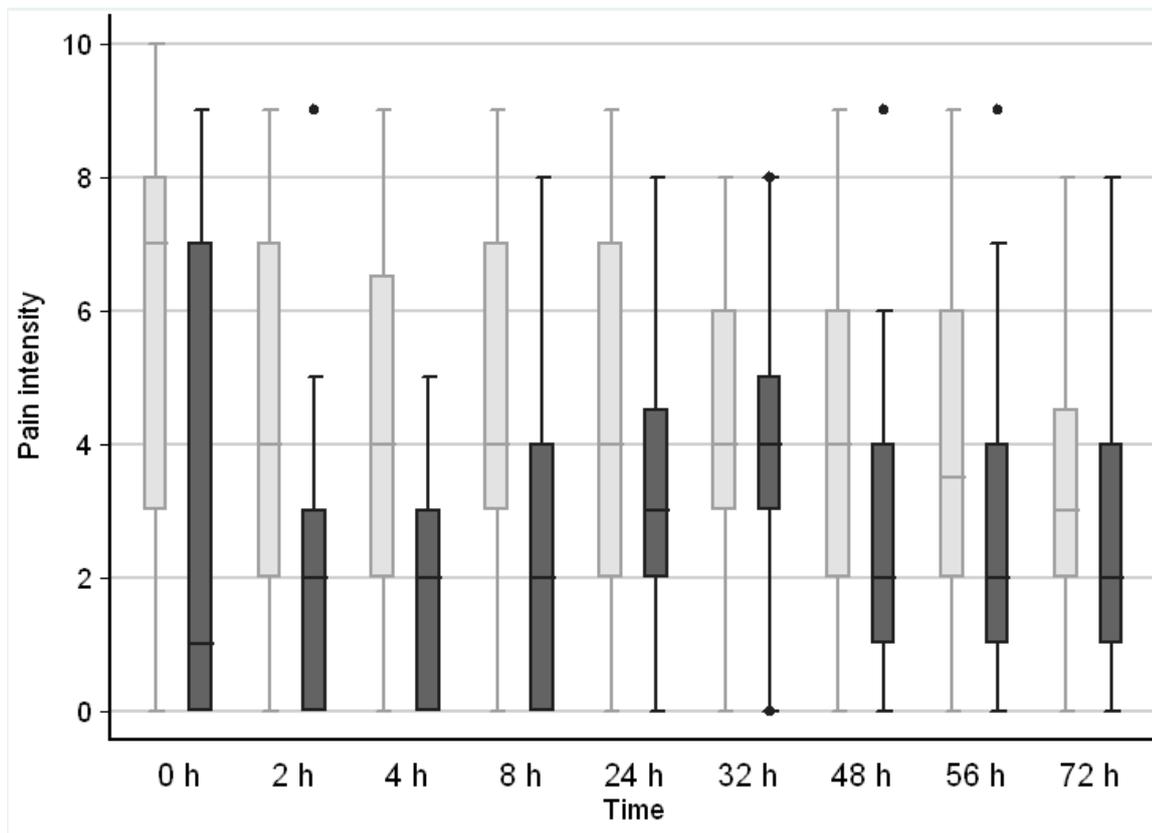
	LIA group (n=30)	ISC group (n=31)
Age, mean (SD) range, years	65 (8) 49-76	66 (8) 53-83
Sex (M/F), n	15/15	9/22
Body mass index, mean (SD), kg/m <sup>2</sup>	29 (5)	30 (6)
Indication		
Osteoarthritis	28	26
Rheumatoid arthritis	1	0
Fracture sequelae	0	5
Cuff arthropathy	1	0
ASA group (I/II/III), n	5/20/5	4/23/4
Preoperative pain score, median (IQR), NRS (0-10)		
At rest (n=27/n=26)	4 (3-6)	5 (2-7)
During activity (n=27/n=25)	8 (7-9)	8 (7-9)
Preoperative daily analgesic use, n (may be several)		
None	2	6
Paracetamol	16	13
NSAID	11	10
Opioid	10	9
Other/Missing	1	4
Type of prosthesis, n		
Total replacement		
Bigliani/Flatow (Zimmer)	13	18
Global Advantage (DePuy Synthes)	1	0
Humeral head replacement		
Bigliani-Flatow (Zimmer)	3	7
Global Advantage (DePuy Synthes)	5	3
Resurfacing		
Global cap (DePuy Synthes)	6	1
Promos (Smith & Nephew)	2	2
Supplemental surgery		
Biceps tenotomy	7	6
Biceps tenodesis	8	8
Other	7	4
Center, n		
Horsens Regional Hospital	18	21
Aarhus University Hospital	12	10

LIA: Local infiltration analgesia. ISC: Interscalene brachial plexus catheter. ASA: American Society of Anesthesiologists physical status. NRS: Numeric rating scale.

**Table II** Postoperative opioid consumption.

Time period	LIA group	ISC group	<i>P</i> -value
<b>First 24 hours after surgery (n=30 / n=31)</b>	<b>95 (70-150)</b>	<b>40 (8-76)</b>	<b>0.0001</b>
Day 0 to 3 overall (n=17 / n=19)	199 (120-245)	103 (50-213)	0.06
Day 0 (n=30 / n=31)	76 (59-99)	17 (0-63)	<0.001
During stay in PACU (n=30 / n=31)	60 (36-90)	0 (0-49)	0.001
Remainder of day 0 (n=30 / n=31)	15 (10-30)	0 (0-10)	<0.001
Day 1 (n=26 / n=27)	35 (20-70)	30 (13-60)	0.41
Day 2 (n=19 / n=24)	33 (20-50)	20 (0-41)	0.13
Day 3 (n=18 / n=19)	30 (20-50)	20 (10-50)	0.54

In oral morphine equivalents, median (IQR), in mg. LIA: Local infiltration analgesia. ISC: Interscalene brachial plexus catheter. PACU: Postoperative care unit.

**Figure 2** Postoperative pain intensity by Numeric Rating Scale (NRS, 0-10).

Light grey: Local infiltration analgesia group. Dark grey: Interscalene brachial plexus catheter group.



Paper II:  
Dexamethasone for pain after outpatient shoulder surgery: a  
randomized, double-blind, placebo-controlled trial

# Dexamethasone for pain after outpatient shoulder surgery: a randomised, double-blind, placebo-controlled trial

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**Background:** Dexamethasone has analgesic properties when given intravenously before surgery, but the optimal dose has not been determined. We hypothesised that a dose of 40 mg dexamethasone would improve analgesia after outpatient shoulder surgery compared with 8 mg.

**Methods:** A randomised, double-blind, placebo-controlled clinical trial was conducted at Horsens Regional Hospital, Denmark. Patients scheduled for arthroscopic subacromial decompression and/or acromioclavicular joint resection as an outpatient procedure ( $n = 101$ ) were randomised to receive intravenous dexamethasone 40 mg (D40), 8 mg (D8) or placebo (D0) before surgery. The primary outcome was pain intensity 8 h after surgery rated on a numeric rating scale of 0 to 10. Secondary outcomes were pain intensity, analgesic consumption and side effects during the first 3 days after surgery.

**Results:** Data from 73 patients were available for analysis: (D40: 25, D8: 26, D0: 22 patients). Eight hours after surgery, pain inten-

sity were: [median (interquartile range)] group D40: 2 (1–4), group D8: 2.5 (1–5), group D0: 4 (2–7). There was no significant difference in pain intensity between group D40 and D8 after 8 h ( $P = 0.46$ ) or at any other time. When comparing all three groups, a statistically significant dose–response relationship was seen for present, average and worst pain intensity after 8 h and on the following morning. No differences were found in analgesic consumption. No serious side effects were observed.

**Conclusion:** Although our data supported a dose–response relationship, increasing the dexamethasone dose from 8 to 40 mg did not improve analgesia significantly after outpatient shoulder surgery.

Accepted for publication 2 April 2014

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THE use of dexamethasone for the prophylaxis of post-operative nausea and vomiting (PONV) is well documented.<sup>1–3</sup> Dexamethasone also has analgesic properties; however, the optimal dose has not been determined. A meta-analysis of the use of dexamethasone for analgesia after various surgical procedures showed a reduction of post-operative pain and opioid consumption if doses above 0.1 mg/kg were used.<sup>4</sup> Doses ranged from 4 to 80 mg dexamethasone, but only two studies used doses above 20 mg, which limits conclusions about the effect of higher doses. Another recent meta-analysis based on 5796 patients who received dexamethasone 1.25–20 mg after various surgical procedures showed a small dose–response effect on pain after 24 h, and further dose–response studies were called for.<sup>5</sup> As the analgesic effect of dexamethasone is most likely

caused by inhibition of inflammation and surgical stress response, the optimal dose could depend on the extent of the surgery.<sup>1</sup> This could contribute to weak conclusions in meta-analyses that include different surgeries.

In major and minor orthopaedic surgery, dexamethasone and other glucocorticoids have demonstrated analgesic effect in dexamethasone-equivalent doses ranging from 9 to 40 mg.<sup>6–11</sup> In shoulder surgery, only very limited data are available, but dexamethasone 4–8 mg has been used as an adjuvant in interscalene blocks with prolonged analgesic effect.<sup>12–16</sup> This could be due to a systemic effect because both intravenous (i.v.) and perineural administration of dexamethasone have been shown to increase the analgesic duration of the block.<sup>17</sup>

In comparison with the perioperative doses, the usual dose of corticosteroid used for local injection in the shoulder region for diagnostic or therapeutic

Trial Registry: <http://clinicaltrials.gov/> identifier: NCT01414569.

purposes corresponds to dexamethasone 8–16 mg.<sup>18</sup> Also in comparison, the maximal physiological cortisol production rate is approximately 225 mg/day, which corresponds to 8.5 mg/day of dexamethasone.<sup>19,20</sup> Although higher perioperative doses have been used,<sup>10</sup> we estimated the highest possible dose of interest for this minor surgery to be 40 mg.

The effect of dexamethasone lasts at least 24 h,<sup>5</sup> which makes it ideal for single-dose administration prior to outpatient surgery because pain after discharge is often undertreated.<sup>21</sup> Arthroscopic subacromial decompression (ASD) and arthroscopic acromioclavicular joint resection (ACR) are performed for impingement and osteoarthritis of the acromioclavicular joint, respectively. The two procedures are quite uniform and entail a similar degree of post-operative pain.

We hypothesised that an increase of the dexamethasone dose from our currently used anti-emetic dose of 8 mg to a high dose of 40 mg would significantly improve analgesia after discharge following outpatient ASD and ACR. A placebo group was included for secondary comparison.

## Methods

### *Patients and design*

This was a double-blind, parallel group, placebo-controlled, randomised clinical trial conducted at the Centre of Day Surgery, Horsens Regional Hospital, Denmark. The study was registered at <http://clinicaltrials.gov/> (identifier NCT01414569), approved by the Central Denmark Region Committee on Health Research Ethics (M-20110188, 24 August 2011, address: Skottenborg 26, DK-8800 Viborg), the Danish Data Protection Agency, and the Danish Health and Medicines Authority (EudraCT no. 2011-003082-15), and monitored by the Good Clinical Practice (GCP) unit of Aarhus University Hospital to ensure compliance with the standards of GCP.

Inclusion criteria were scheduled ASD and/or ACR as outpatient surgery. Primary exclusion criteria were planned nerve block, concomitant other surgery, age below 18 or above 90 years, allergy to dexamethasone, glaucoma, untreated hypertension, diabetes, daily use of glucocorticoids, daily use of strong opioids and daily use of analgesics for reasons other than shoulder pain. A secondary exclusion criterion was more extensive surgery than planned such as repair of rotator cuff or labrum, biceps tenodesis or arthrolysis. In cases of secondary exclusion, 'mirror-randomisation' was used, and the

new patient received the same number as the excluded patient with the letter A added. Patients received oral and written information about the study from the surgeon when the decision to operate was made and were later telephoned by Karen Toftdahl Bjørnholdt or assistants for a preliminary oral consent. Written consent was obtained on the day of surgery from all participants.

### *Intervention, randomisation and blinding*

The study drug was 43.72 or 8.74 mg dexamethasone dihydrogen phosphate-disodium corresponding to 40 or 8 mg dexamethasone-21-dihydrogen phosphate [Fortecortin (TM), Merck Serono, Darmstadt, Germany] provided by the pharmacy at Aarhus University Hospital. A randomisation list was generated by the pharmacy using five randomly permuted blocks of 15 patients (<http://www.randomization.com/>). Numbered dosage bags of the study drug or placebo in 100 ml saline were prepared according to the randomisation list and delivered from the pharmacy. The bags were identical in appearance, and the staff, patients and data collectors were blinded. The randomisation list was stored at the pharmacy until all patients had been included and the follow-up was completed. As soon as possible upon arrival at the Centre of Day Surgery, patients were given i.v. dexamethasone 40 mg (D40), dexamethasone 8 mg (D8) or placebo (D0) infused over approximately 10 min.

### *Standard protocol for anaesthesia and surgery*

Pre-operatively, all patients received paracetamol 1 g orally; patients with an increased risk of gastrointestinal ulcer or daily prophylactic treatment with proton pump inhibitors, also received pantoprazol 40 mg or the usual treatment. Anaesthesia was induced with propofol 2–3 mg/kg and remifentanyl 1 µg/kg, and a laryngeal mask was inserted. Anaesthesia was maintained by continuous infusion of propofol 2.5–3 mg/kg/h and remifentanyl 1 µg/kg/min (approximate infusion rates), and the patients' lungs were ventilated with 50% oxygen in air. I.v. fentanyl 50–100 µg and ketorolac 30 mg were administered near the end of surgery, unless contraindicated. I.v. ondansetron 4 mg was also administered near the end of surgery to patients with an increased risk of PONV (fulfilling two out of the following four criteria: female < 50 years, non-smoker, expected to require post-operative opioids, previous PONV/motion sickness).

Surgery was arthroscopic using two or three portals and both the glenohumeral joint and

subacromial space were examined. Bupivacaine 5 mg/ml with adrenaline was distributed in the glenohumeral joint, subacromial bursa and for blocking of the suprascapular nerve at the beginning (15–20 ml) and end of surgery (15–20 ml). Surgery was performed by one of seven experienced surgeons.

### *Post-operative treatment*

In the recovery room, ice packs were applied around the shoulder. PONV was treated with i.v. ondansetron 4 mg. Study patients were offered i.v. fentanyl 50 µg if pain exceeded 3 on a numeric rating scale (NRS; 0, no pain, and 10, worst pain possible). Oral post-operative analgesic treatment was started before discharge from the recovery room and consisted of paracetamol 1 g every 4 h up to 4 g daily and, as rescue medication, ibuprofen 600 mg up to 1800 mg daily (for moderate pain) and morphine 10 mg up to 60 mg daily (for severe pain). If ibuprofen or morphine was contraindicated, the drug in question was replaced by tramadol 50–100 mg up to 400 mg daily. Patients were discharged directly from the recovery room and were provided these rescue analgesics to use at home.

Thus, dexamethasone was added to a multimodal analgesic regimen of local anaesthetics and systemic paracetamol, non-steroidal anti-inflammatory drugs and opioids.

### *Data collection*

Data were obtained from the medical records and by means of a questionnaire developed for the present study. Patients were asked to rate their present pain intensity (NRS, 0–10) before surgery, on awakening from anaesthesia, at discharge from the recovery room, 8 h after surgery and at 8 a.m. and 8 p.m. ending on the morning of the third post-operative day. Worst and average pain intensity scores since the last reporting were also reported at 8 h after surgery and at 8 a.m. and 8 p.m. thereafter. Analgesic medication after discharge was reported in the questionnaire by patients when it was taken, with the time of day, name of drug and dose. Patients also reported side effects (open and closed questions) on the third post-operative day. Complications such as infection or delayed wound healing were assessed after 2 months at the outpatient follow-up with a hospital physiotherapist or by telephone.

The primary outcome measure was present pain intensity (NRS, 0–10) 8 h after surgery. Secondary outcomes were pain intensity, analgesic consump-

tion and side effects recorded for 3 days after surgery.

### *Statistical analysis*

The sample size was calculated based on the hypothesis that dexamethasone 40 mg would reduce pain intensity by two points on the NRS (0–10) 8 h after surgery compared with dexamethasone 8 mg. A difference of less than two points was considered not to be of clinical relevance. Given a standard deviation of 2.3 (based on a pre-trial validation of the questionnaire),  $\alpha = 0.05$  and  $\beta = 0.2$ , the required number of patients was 21 in each group. It was decided to include 25 patients in each group to allow for dropouts.

Data obtained from medical records and patient questionnaires were digitalised using EpiData, version 3.1 (EpiData Association, Odense, Denmark). Opioids were converted to oral morphine equivalents according to relative potency<sup>22</sup> [(all in mg, oral morphine : other): 3 : 1 i.v. morphine; 300 : 1 i.v. fentanyl; 0.3 : 1 i.v. pethidine; 0.1 : 1 oral tramadol; and 1.5 : 1 oral oxycodone]. Data were analysed partly by intention-to-treat, so that protocol violations did not exclude patients from analysis. However, patients who met the secondary exclusion criteria were excluded from the analysis, as were patients who did not receive the study drug or failed to return the questionnaire. Missing values were not constructed to expected values, but the analysis was based on the available data (without the rest of the patient's data being excluded from other analyses). The primary data analysis was blinded with respect to the two active treatment groups, only revealing which of the three groups was placebo. Analyses comparing outcomes in groups D40 and D8 were performed using Mann–Whitney *U*-test/Kruskal–Wallis test because of skew distributions for all outcomes and ordinal scales for pain intensity and side effects [presented as median with lower and upper interquartile range (IQR)]. For analyses of dose–response, Spearman's rank correlation coefficient was used.  $P < 0.05$  was considered statistically significant. Statistical analyses were conducted using Stata software version 12 (StataCorp, College Station, TX, USA).

## **Results**

Patients were included from November 2011 to April 2013. The participant flow is shown in the flow diagram (Fig. 1). Seventeen patients were excluded because of more extensive surgery: cuff repair (11),

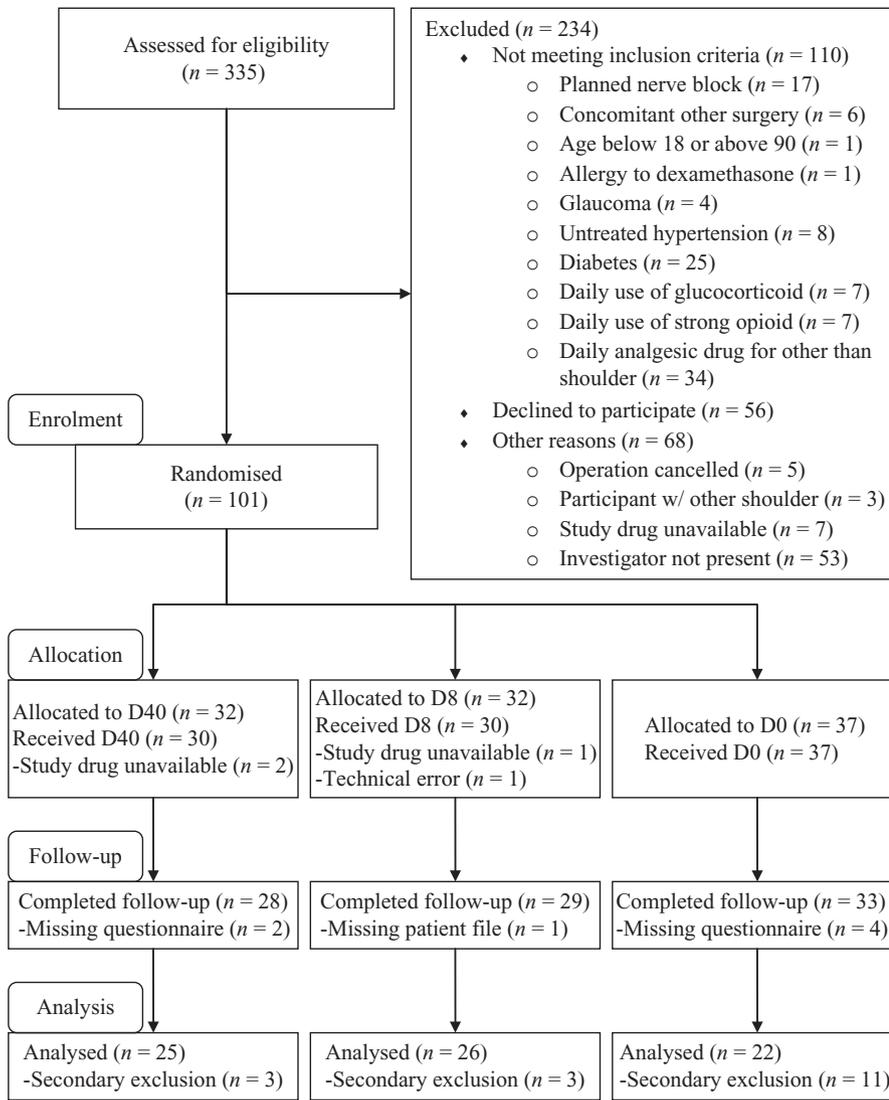


Fig. 1. Flow diagram. D40: dexamethasone 40 mg, D8: dexamethasone 8 mg, D0: placebo, n, number of patients.

labral repair (3), arthrolysis (2) and tenodesis (1). Patient characteristics are shown in Table 1.

The primary outcome of pain intensity 8 h after surgery was [median (IQR)]: group D40: 2 (1–4), group D8: 2.5 (1–5), group D0: 4 (2–7). There was no significant difference in pain intensity between group D40 and D8 after 8 h ( $P = 0.46$ ) or at any other recording time. When all three groups were included in analysis, there was a significant correlation between dose and pain intensity for present ( $P = 0.021$ ), worst ( $P = 0.005$ ) and average ( $P = 0.035$ ) pain scores after 8 h (Figs 2 and 3). This was also the case for present ( $P = 0.034$ ), worst ( $P = 0.007$ ) and average ( $P = 0.006$ ) pain scores on the morning of the first post-operative day as well as worst ( $P = 0.046$ ) pain scores on the evening of the first post-operative day (Figs 2 and 3). In a pairwise comparison, signifi-

cant differences were only found between group D40 and D0 for these same time points, except the evening of the first post-operative day, and for group D8 and D0 for worst pain intensity after 8 h. Pain intensity at other time points was not significantly different between groups.

Consumption of opioids (converted to oral morphine equivalents) and ibuprofen was similar in the three groups (Table 2). The opioids used post-operatively were i.v. fentanyl (group D40:  $n = 12$ , group D8:  $n = 13$ , group D0:  $n = 12$ ), oral morphine (group D40:  $n = 14$ , group D8:  $n = 13$ , group D0:  $n = 16$ ) and oral tramadol (group D40:  $n = 5$ , group D8:  $n = 5$ , group D0:  $n = 5$ ). One patient in group D0 received i.v. morphine and pethidine in the recovery room, and one patient in group D40 received oral oxycodone after discharge, prescribed by his

Table 1

Baseline characteristics and pre-operative and perioperative data.

	Dexamethasone 40 mg (n = 25)	Dexamethasone 8 mg (n = 26)	Placebo (n = 22)
<b>Patient characteristics</b>			
Age (years)	53 (10)	55 (11)	49 (11)
Sex (male/female)	11/14	12/14	12/10
Weight (kg)	80 (14)	78 (13)	91 (18)
Height (cm)	172 (10)	173 (10)	177 (10)
ASA group (I/II)	14/11	13/13	8/14
Operated side (right/left)	18/7	13/13	14/8
<b>Pre-operative data</b>			
Pain at rest (0–10)	6 (4–8)	5 (3–6)	5 (3–8)
Pain during activity (0–10)	8 (6–9)	7 (5–9)	7.5 (6–9)
<b>Daily consumption of</b>			
Paracetamol	15	15	10
NSAID	8	5	7
Tramadol	6	3	3
<b>Perioperative data</b>			
Time from infusion of drug to surgery start (min)	40 (20–72)	60 (40–90)	28 (20–60)
Type of surgery (ASD/ACR/both/other)	7/0/18/0	10/5/10/1	5/4/12/1
Duration of surgery (min)	56 (13)	56 (16)	55 (14)

Presented as mean (SD), median (IQR) or count as appropriate.

ACR, acromioclavicular joint resection; ASA, American Society of Anaesthesiologists physical status; ASD, arthroscopic subacromial decompression; NSAID, non-steroidal anti-inflammatory drugs.

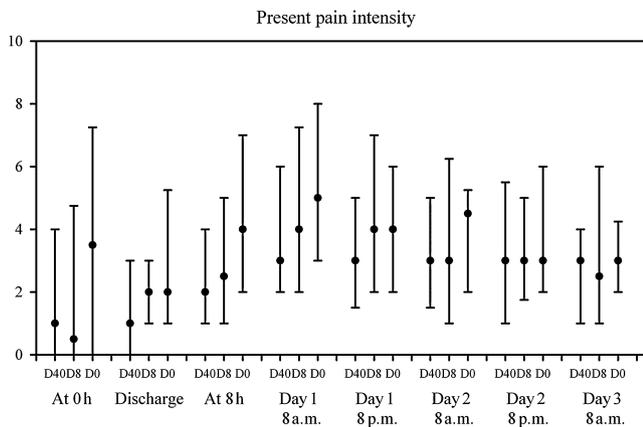


Fig. 2. Present pain intensity. D40: 40 mg dexamethasone group, D8: 8 mg dexamethasone group, D0: placebo group.

general practitioner. The length of stay in the recovery room was also similar in the three groups, mean (range) in h: group D40 2 : 24 (1 : 15–4 : 40), group D8 2 : 25 (1 : 10–3 : 45) and group D0 2 : 41 (0 : 35–6 : 45) ( $P = 0.84$ ).

The side effects questioned directly are shown in Fig. 4. The incidence of nausea was similar between groups as expected because of treatment with ondansetron. Groups D40 and D8 showed a non-significant trend towards more stomach pain or discomfort, less fatigue and less bruising than group D0. In reply to the open question regarding side effects,

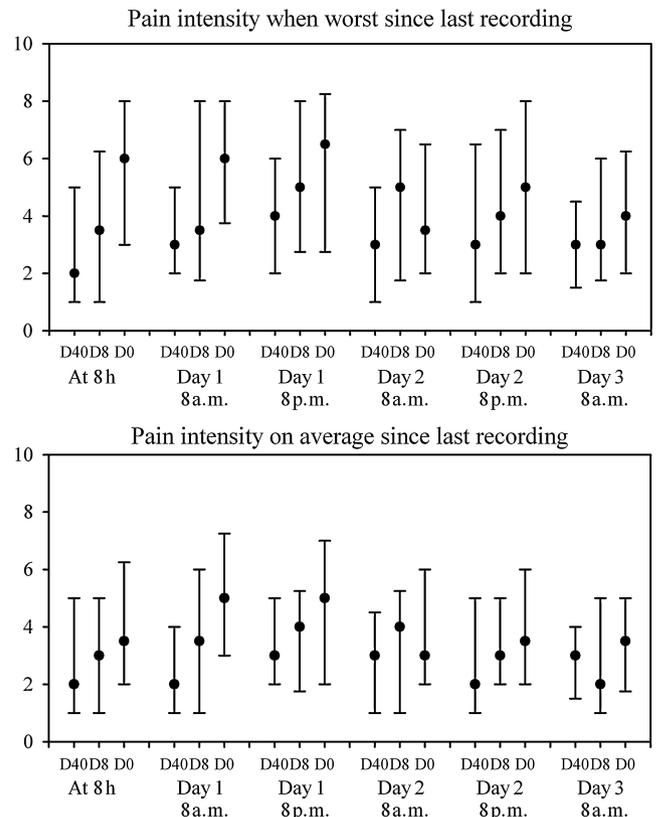


Fig. 3. Worst and average pain intensity. D40: 40 mg dexamethasone group, D8: 8 mg dexamethasone group, D0: placebo group.

Table 2

Consumption of analgesics in mg, as median (interquartile range).				
	Dexamethasone 40 mg (n = 25)	Dexamethasone 8 mg (n = 26)	Placebo (n = 22)	P-value
<b>Opioids</b>				
From surgery to discharge	10 (0–30)	12.5 (0–25)	20 (0–40)	0.62
From surgery to 24 h	20 (0–50)	27.5 (0–45)	30 (10–50)	0.77
From surgery to day 3	45 (0–100)	42.5 (10–100)	45 (10–70)	0.97
<b>Ibuprofen</b>				
From surgery to 24 h	600 (0–1800)	900 (0–1800)	1200 (600–2400)	0.44
From surgery to day 3	2400 (600–4600)	2700 (600–4200)	3600 (600–4800)	0.58

Opioids as oral morphine equivalents. Kruskal–Wallis test.

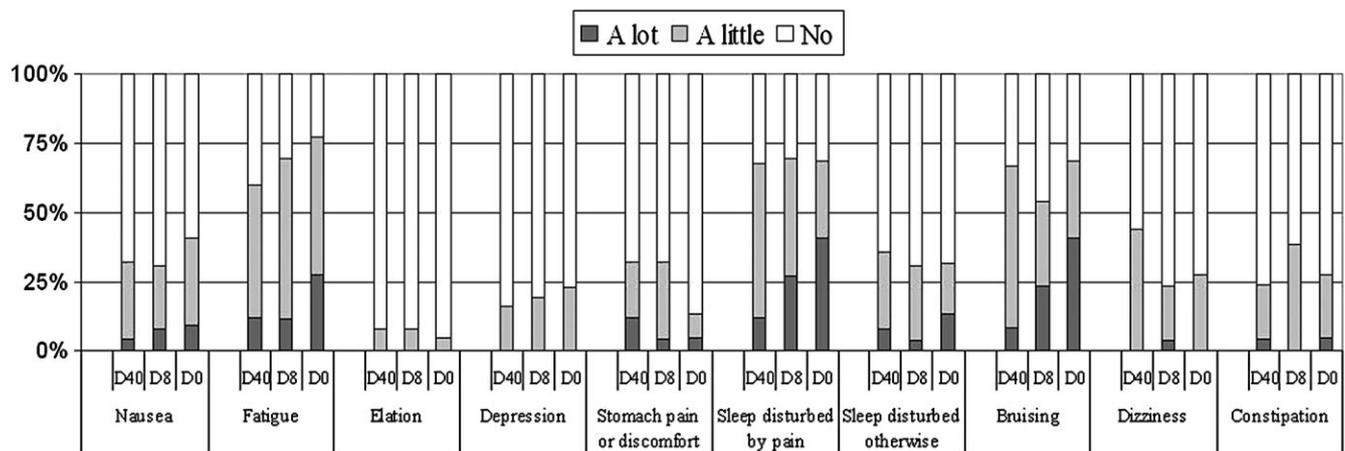


Fig. 4. Patient-reported side effects. D40: 40 mg dexamethasone group, D8: 8 mg dexamethasone group, D0: placebo group. No significant differences between groups by Kruskal–Wallis test.

two patients in group D40 reported internal unrest and inability to sleep the first night after surgery. Heartburn was reported by two patients (group D40 and D8). One patient fainted the night after surgery (group D40), one patient fainted the second day after surgery (group D8) and one patient experienced unrest and fear of fainting (group D0). None of the patients experienced perineal symptoms during infusion of dexamethasone or placebo. No patients had infections or delayed wound healing.

A few protocol violations occurred. Two patients (group D8) received oral dexamethasone 8 mg similar to the regular patients at the Centre of Day Surgery in addition to the study drug. Also, three patients (one in group D40; two in group D8) received daily analgesics for other purposes than the shoulder and should have been excluded during screening of eligible patients. In two patients (group D8 and D0), the planned decompression turned out not to be necessary and only the subacromial bursa was removed. One patient (group D0) received an

interscalene block in the recovery room because of pain. Suxamethonium and alfentanil were used to facilitate rapid sequence induction of anaesthesia and orotracheal intubation in three patients (one in group D40; two in group D8). These protocol violations did not lead to exclusion from the analysis; however, a per-protocol analysis without these participants decreased power but provided similar results.

### Discussion

In this study of outpatient shoulder surgery, an increase of the dexamethasone dose from 8 to 40 mg did not significantly decrease pain intensity or consumption of analgesics. In comparison with two systematic reviews<sup>4,5</sup> in which the estimated mean difference in pain intensity (dexamethasone vs. placebo) was around 0.5, we found a rather large reduction in pain intensity after 8 h from a median NRS score of 4 (group D0) to 2.5 (group D8) and 2

(group D40). This reduction is in accordance with other studies conducted with doses of 9 or 10 mg in orthopaedic patients.<sup>7,23</sup> Our dose–response estimation is consistent with a report of dexamethasone 4 mg not providing significant analgesia,<sup>24</sup> which again is in accordance with the review<sup>4</sup> recommending doses above 0.1 mg/kg.

Some limitations of the present study should be considered. First, it can be argued that the number of included patients was too low. As intended, our sample size was sufficient to detect what we considered to be a clinically relevant difference in pain intensity of two points on the NRS (0–10) with a risk of type-2 error of 0.2. Our results for groups D40 and D8 were far from reaching this difference in pain intensity and likewise a clinically relevant difference in analgesic consumption. Therefore, if a dose of 40 mg should be superior to a dose of 8 mg, our results illustrate that any such difference is highly likely to be too small to be of clinical interest. Second, the analgesic consumption was calculated on the basis of different types of opioids because different types were administered in the recovery room and after discharge according to the existing departmental guidelines and the patients' usual medication. The analysis of analgesic use would have been more accurate if only one type of opioid had been included, thereby avoiding possible errors in the transformation factors. Third, the use of a basic analgesic regimen may have obscured the effect of the study medication and reduced the study sensitivity considerably. However, we found it ethically problematic to limit the use of analgesics, including rescue ibuprofen and morphine, as a pilot study conducted in the same source population (given dexamethasone 8 mg) showed a mean NRS of five 8 h after surgery. As it turned out in this study, pain ratings in group D8 were not as high as predicted. Fourth, it would have been an advantage if the same surgeon had performed all the operations to increase the uniformity of the procedure. The surgeons were evenly distributed over the three groups, which reduced confounding, but the involvement of seven surgeons could contribute to a greater uncertainty. Finally, due to the short period of time between the arrival at the Centre of Day Surgery and the time of operation, the drug could not be given 1–2 h before surgery as often recommended. The drug was administered at mean (range) 54 min (–5 to 2: 55) before surgery (Table 1). No association was found between the time of administration and pain intensity on awakening or at discharge, or opioid consumption in recovery.

Although these limitations exist, the study is distinguished by successful randomisation, blinding and adherence to the principles of GCP.

No serious side effects were observed. Some patients had stomach pain or discomfort, and two reported heartburn (group D40 and D8), which may be a cause for concern regarding the risk of gastric complications. None of the patients experienced perineal pruritus or hypertensive crisis, as previously reported,<sup>4,25</sup> probably due to the infusion over 10 min. The study is too small to assess the risk of rare events such as fainting, but this did occur. A large study concerning the safety of very high-dose dexamethasone (1 mg/kg) in patients undergoing cardiac surgery found no increase in mortality, myocardial infarction, stroke or renal failure.<sup>26</sup> However, bleeding, gastric complications, wound healing, treatment consequences in diabetic patients or patient reported outcomes such as sleep quality, mental side effects or fatigue were not assessed. These outcomes should be further investigated to assess the benefit vs. harm for dexamethasone use in outpatient surgery.

The duration of pain beyond the first 3 days and the time before returning to normal daily activities were not examined. Although given in a single dose, dexamethasone could influence these outcomes or the risk of developing frozen shoulder or chronic post-operative pain. Future studies should include these functional and longer term outcomes. Finally, these results cannot uncritically be extrapolated to other glucocorticoids, as their relative potency has been established with regard to the glucocorticoid, anti-inflammatory or sodium-retaining effects,<sup>27</sup> not the analgesic effect that may not solely be due to the anti-inflammatory effect.<sup>28</sup>

In summary, we found that although our data support a dose–response relationship, increasing the dose of dexamethasone from 8 mg to 40 mg did not increase the analgesic effect significantly in minor outpatient shoulder surgery when added to a multimodal analgesic regimen.

## Acknowledgements

We wish to thank the staff at the Centre of Day Surgery for their extra efforts, and project nurses Gitte Ellemose Vinther, Johanna Strohbach and Mette Blichfeldt Kofod for help with inclusion and data collection.

*Conflict of interest:* The authors have no conflicts of interest.

*Funding:* This work was supported by the Health Research Fund of Central Denmark Region, The Family Hede Nielsen Foundation, The Danish Rheumatism Association and the Augustinus Foundation.

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Paper III:

Persistent pain is common 1–2 years after shoulder replacement. A nationwide registry-based questionnaire study of 538 patients

# Persistent pain is common 1–2 years after shoulder replacement

## A nationwide registry-based questionnaire study of 538 patients

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Submitted 2014-08-06. Accepted 2014-10-17.

**Background and purpose** — Persistent postsurgical pain is a well-recognized problem after various types of surgery such as amputation and thoracotomy. The prevalence of persistent pain, and the extent to which it involves neuropathic pain, is highly dependent on the type of surgery. We investigated the prevalence of, characteristics of, and risk factors for persistent pain 1–2 years after shoulder replacement.

**Patients and methods** — A questionnaire was sent to patients who underwent primary shoulder replacement between April 2011 and April 2012, and whose data were recorded in the Danish Shoulder Arthroplasty Register. Patients who had undergone reoperation or bilateral replacements were excluded. Persistent pain was defined as constant or daily pain within the last month, which interfered much or very much with daily activities. Multivariate logistic regression was used to assess risk factors.

**Results** — 538 patients were available for analysis. The prevalence of persistent pain was 22% (CI: 18–25), and the prevalence of presumed neuropathic pain was 13% (CI: 10–16). Persistent pain was more frequent in fracture patients (29%) than in osteoarthritis patients (16%), while the prevalence of neuropathic pain was similar. Severe pain during the first postoperative week increased the risk of persistent pain. Risk also increased with hemiprosthesis (as compared to total prosthesis) in osteoarthritis patients, and with previous osteosynthesis and pain elsewhere in fracture patients.

**Interpretation** — Persistent pain after shoulder replacement is a daily burden for many patients. Further studies should address patient and prosthesis selection, postoperative pain management, and follow-up of these patients.

There is a substantial amount of literature documenting that there is a possible risk of persistent pain after almost any surgical procedure (Macrae 2001, Johansen et al. 2012). The prevalence rates are highly dependent on the type of surgery, and vary from 5% to 85% (Kehlet et al. 2006, Macrae 2008). The consequences of chronic or persistent postsurgical pain are significant, not only in terms of suffering and reduced quality of life for the individual patient, but also with regard to the subsequent costs to healthcare services and social services. Many authors have reported putative risk factors for persistent pain, including genetic factors, age, psychosocial factors, type of anesthesia, pain elsewhere than the surgical site, other comorbidities, preoperative pain, and acute postoperative pain (Althaus et al. 2012, VanDenKerkhof et al. 2013). Intraoperative nerve damage and the extent of surgery are also important risk factors (Katz and Seltzer 2009). In fact, many patients with persistent postsurgical pain present with characteristic symptoms of neuropathic pain in the affected area (Kehlet et al. 2006).

There is a scarcity of data on persistent postsurgical pain after orthopedic surgery. To our knowledge, previous studies focusing on persistent postsurgical pain in orthopedic patients have concerned mainly amputation or hip or knee replacement (Nikolajsen et al. 2006, Lundblad et al. 2008, Beswick et al. 2012, Liu et al. 2012, Jansen et al. 2014). Trials of shoulder replacement surgery have more commonly reported pain relief, or a composite score including pain, rather than the prevalence of pain at follow-up. There has been very little research on predictive factors for persistent postsurgical pain following shoulder replacement, but the general outcome has been shown to be associated with diagnosis and prosthesis type (Radnay et al. 2007, Fevang et al. 2013) and with previous shoulder surgery, age, and preoperative Short Form-36 mental

score and DASH functional score (Simmen et al. 2008). Identification of subgroups at increased risk is important in order to establish interventions to prevent or minimize the impact of persistent postsurgical pain.

We investigated the prevalence of, the characteristics of, and risk factors for persistent pain 1–2 years after more than 500 shoulder replacements performed in Denmark.

## Material and methods

This was a cohort study in which the baseline data were retrieved from the Danish Shoulder Arthroplasty Register (DSR) (Rasmussen et al. 2012) and the follow-up data were obtained using a patient questionnaire.

### Patients

All patients were recruited from the DSR (see description below). For this study, the inclusion criteria were primary shoulder replacement between April 1, 2011 and April 1, 2012, and age above 18 years. Exclusion criteria were prosthesis in the contralateral shoulder and any type of reoperation. Patients who met these criteria were sent a questionnaire on May 30, 2013. A reminder was sent after 25 days to all patients who did not reply. Thus, the length of follow-up was 14–26 months. In order to reduce response bias, patients were strongly urged to respond regardless of whether they had experienced pain or not. The size of the study was determined indirectly by the number of patients in the registry who matched our criteria.

### Questionnaire data

The questionnaire was in Danish and was developed especially for the study, as no suitable pre-existing questionnaire was found. Based on the literature and the experience of the authors, the questionnaire was drafted and assessed by research peers. After revision, the questionnaire was piloted in a group of 10 patients who had undergone shoulder replacement at the first author's institution. After evaluation of the responses, the final questionnaire was drawn (see the translated questionnaire in Supplementary data). The questionnaire included questions to assess (1) inclusion and exclusion criteria, (2) current pain characteristics and pain treatment, (3) neuropathic pain characteristics (DN4: Douleur Neuropathique, 4 questions) (Bouhassira et al. 2005), and (4) possible predictors of persistent pain (pain elsewhere, height and weight, preoperative and acute postoperative pain). The outcome of persistent pain was defined as pain experienced every day or constantly within the last month at a level that interfered much or very much with daily activities. Recall bias was expected for the questions concerning preoperative pain and acute postoperative pain. To minimize this bias, a verbal rating scale (none/mild/moderate/severe) was used instead of a numerical rating scale, and the period in question was limited to the week before/after surgery.

### Registry data

The DSR was established in 2004. The DSR included 91% and 92% of all shoulder replacements performed in Denmark in 2011 and 2012, respectively (DSR annual report 2013). It collects reports by the surgeons at the time of the operation, and patients are routinely contacted by the registry after 1 year to complete the Western Ontario Osteoarthritis of the Shoulder Index (WOOS) (Lo et al. 2001, Rasmussen et al. 2013) with 2 supplementary questions. Data extracted from the registry included age, sex, diagnosis, prosthesis, previous shoulder surgery, supplementary surgery, and patient-reported data. Patient names, updated addresses, and status (e.g. death, emigration) were retrieved from the Danish Civil Registration System and matched to the registry data by means of the civil registration number.

### Statistics

Data from the questionnaires were entered manually into Epidata version 3.1. They were then merged with registry data for analysis in Stata software version 12. Missing data were not constructed to expected values, and the analysis was based on the data available. Patients were not included in the final analysis if their dataset was incomplete for the grouping variables (questions 8 and 11) and the following predictive factors used in the regression: age, sex, diagnosis, prosthesis type, pain elsewhere, and severity of acute postoperative pain. For patients who had returned their questionnaires with these crucial data missing, and who had accepted to be contacted again, we obtained the missing data by telephone interview or e-mail. Descriptive statistics are presented as counts (with %), as mean (with SD) for normally distributed data, or as median (with interquartile range (IQR)) for data that were not normally distributed. Confidence intervals (CIs) for prevalence are calculated as exact binomial 95% CI (Clopper-Pearson). Analyses for association with persistent pain in Table 2 and for generalizability were performed by t-test, chi-squared test, or Wilcoxon rank-sum test as appropriate. Any p-value of less than 0.05 was considered statistically significant. A multivariate logistic regression model was used to assess whether selected factors predicted the outcome of pain at follow-up. Factors were considered suitable for inclusion in the risk factor analysis if they could correct for unknown confounders (age, sex, body mass index) or were clinically relevant and there were enough data to allow inclusion in analysis.

### Ethics

The study was approved by the Danish Data Protection Agency and the committee of the DSR. Studies based on questionnaires or registers do not require approval from the regional or national Committee on Health Research Ethics in Denmark. The study was registered at <http://clinicaltrials.gov/> with identifier NCT01900223.

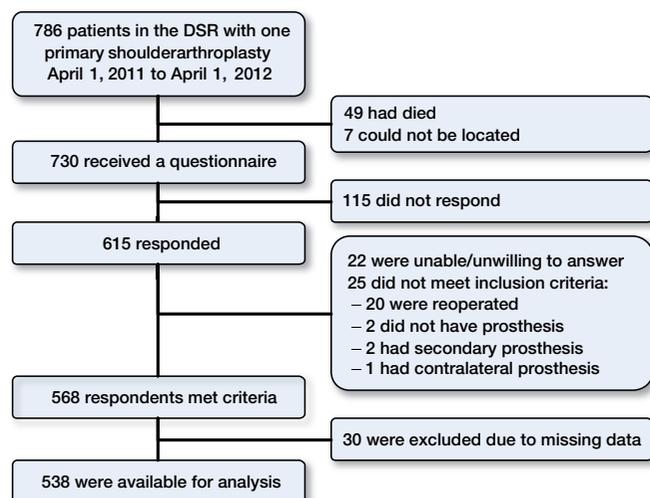


Figure 1. Flow chart of the patients. DSR: the Danish Shoulder Arthroplasty Register.

## Results

The registry contained records of 786 patients with 1 primary shoulder replacement who were operated from April 2011 to April 2012. Replies were received from 615 patients (response rate 78%). Data from 538 patients were available for analysis (Figure 1). Mean follow-up time was 20 (14–26) months.

### Pain status

Persistent pain, defined as pain experienced every day or constantly within the last month at a level that interfered much or very much with daily activities, was present in 117 of 538 patients (22%, CI: 18–25) (Table 1). The prevalence of persistent pain differed between the 2 predominant diagnoses, being present in 66 of 228 patients with fractures (29%, CI: 23–35) and 26 of 226 patients with osteoarthritis (16%, CI: 11–21). Neuropathic pain, assessed by the 7-item DN4 questionnaire, was present in 66 of 505 patients (13%, CI: 10–16). The prevalence of presumed neuropathic pain was similar between diagnoses: 32 of 212 fracture patients (15%, CI: 11–21) and 26 of 212 osteoarthritis patients (12%, CI: 8–17). There was no difference in the length of follow-up between those with persistent pain or presumed neuropathic pain and those without. Analgesics were used daily by 159 of 527 patients (30%) for pain limited to or including the operated shoulder, and a further 67 patients (13%) used analgesics less than once a day for pain limited to or including the operated shoulder. The drugs used were paracetamol (n = 161, 31%), non-steroid anti-inflammatory drugs (n = 59, 11%), opioids (n = 98, 19%), and other kinds (n = 25, 5%). Other analgesics included e.g. gabapentin, pregabalin, tricyclic antidepressants, and anti-epileptics. Non-pharmacological treatment of pain limited to or including the shoulder included physiotherapy (n = 76 of 490, 16%), use of a hot water pool (n = 36 of 490, 7%), acupuncture (n = 20 of 490, 4%) and chiropractic (n = 14 of 490, 3%).

Table 1. Prevalence and characteristics of pain in the shoulder 1–2 years after shoulder replacement. n = 538 unless otherwise stated

	n	%
Frequency of pain during the last month		
none	213	40
not every day	132	25
every day	115	21
constantly	78	14
Average pain intensity in the last month (NRS 0–10), n = 527		
none	199	38
1–3	126	24
4–7	149	28
8–10	53	10
Worst pain intensity in the last month (NRS 0–10), n = 529		
none	197	37
1–3	95	18
4–7	144	27
8–10	93	18
Interference with daily life		
none	210	39
a little	104	19
some	100	19
much	68	13
very much	56	10
Persistent pain <sup>a</sup>	117	22
DN4: Does the pain have one or more of the following characteristics? n = 515		
burning	77	15
painful cold	42	8
electric shocks	112	22
DN4: Is the pain associated with one or more of the following symptoms in the same area? n = 517		
tingling	82	16
pins and needles	92	18
numbness	46	9
itching	42	8
Neuropathic pain: 3/7 items of DN4 interview, n = 505	66	13
Pain present elsewhere		
none	185	34
mild	69	13
moderate	161	30
severe	123	23
Location of the other pain (may be several, n = 532)		
head	9	2
back	147	28
upper extremity	110	21
lower extremity	167	31
stomach	7	1
other	27	5

<sup>a</sup> Persistent pain defined as pain experienced every day or constantly within the last month at a level that interferes much or very much with daily activities.

NRS: numeric rating scale; DN4: Douleur Neuropathique, 4 questions.

For assessment of overall improvement in pain status, patients were asked to compare their current pain to their pain before the operation. However, this was problematic in patients with fractures less than 2 weeks old, who instead often compared their current pain to their pain before the fracture. In the

Table 2a. Persistent pain after shoulder replacement in relation to patient characteristics, surgical data, and complications. n = 538 unless otherwise stated

	All n = 538	Persistent pain at follow-up n = 117	p-value
Mean age at surgery (range)	69 (SD 10) (21–92)	67 (SD 11) (31–91)	0.02
BMI at follow-up, kg/m <sup>2</sup> , mean (n=514) (range)	27 (SD 6) (17–63)	26 (SD 6) (17–47)	0.009

remainder of patients (n = 363), 80% reported being “better” or “much better”, 10% reported no change, and 11% reported being “worse” or “much worse”.

### Persistent pain in relation to registry data and patient-reported complications

Factors associated with the occurrence of persistent pain were age, BMI, diagnosis, previous osteosynthesis, previous cuff reconstruction (marginally), duration of preoperative pain, prosthesis type, supplementary cuff reconstruction, infection, and frozen shoulder (Table 2). Other patient-reported complications included fever, kidney affection, pneumonia, hematoma, thrombosis in the arm, fistula, swelling, complex regional pain syndrome, 3–4 week paralysis of the arm, skin disorder, tight scar tissue, trapped nerve, irritated biceps, and other prosthesis-related complaints (“the prosthesis irritates me” and “it seems as if it is on its way out through the skin”). For patients with persistent pain compared to those without, all items of the WOOS (completed by 392 of the 538 patients) were highly significantly worse by 2-sample Wilcoxon rank-sum (Mann-Whitney) test ( $p < 0.001$  for all items). Persistent pain was especially associated with the 3 emotional items (frustration/discouragement, worry, and feeling like a burden to others), pain with movement, and increased pain after activity.

As diagnosis interacted with other predictors, regression analysis was stratified for fractures and osteoarthritis (Table 3). The other diagnoses were too rare to allow separate regression models. The 2 patient-reported variables used in the regression were dichotomized from 4 categories (none/mild/moderate/severe) due to the number of patients available, so intensity of pain in the first week was dichotomized as “severe” or “other”, and pain elsewhere was dichotomized as “any pain” or “none”. Severe pain during the first postoperative week (experienced by 199 of 538 patients, 37%) was a risk factor regardless of diagnosis of fracture or osteoarthritis. For fractures, previous osteosynthesis and pain elsewhere were predictive of persistent pain. For osteoarthritis, operation with a hemiprosthesis (humeral head replacement) was associated with a higher risk of persistent pain compared to a total prosthesis. Effects of age, sex, and BMI were small or non-existent.

Table 2b. Persistent pain after shoulder replacement in relation to patient characteristics, surgical data, and complications. n = 538 unless otherwise stated

	All n = 538		Persistent pain at follow-up n = 117		p-value
	n	%	n	%	
Sex					0.4
male	165	31	32	19	
female	373	69	85	23	
Diagnosis (may be several)					
arthritis	19	4	1	5	0.08
osteoarthritis	231	43	37	16	0.005
fracture < 2 weeks	157	29	44	28	0.02
fracture > 2 weeks	81	15	26	32	0.01
cuff arthropathy	82	15	11	13	0.05
humeral head necrosis	26	5	10	38	0.03
other	11	2	2	18	0.8
Previous shoulder surgery					
osteosynthesis	25	5	13	52	< 0.001
cuff reconstruction	17	3	7	41	0.05
other	55	10	12	22	1.0
Hospital volume					1.0
1–25 primary SR per year	95	18	21	22	
26–50 primary SR per year	250	46	54	22	
> 50 primary SR per year	193	36	42	22	
Side operated, n = 534					0.9
right	298	56	64	21	
left	236	44	52	22	
Duration of preoperative pain n = 377 <sup>a</sup>					0.04
more than 6 months	318	84	55	17	
6 months or less	59	16	18	31	
Preoperative pain intensity n = 368 <sup>a</sup>					0.05
severe	233	63	52	22	
none/mild/moderate	135	37	19	14	
Prosthesis					
resurfacing	96	18	17	18	0.3
hemi	274	51	75	27	0.001
total	47	9	3	6	0.008
reverse	121	22	22	18	0.3
Supplementary surgery (may be several)					
cuff reconstruction	96	18	30	31	0.01
acromioplasty	7	1	2	29	0.7
acromioclavicular resection	11	2	2	18	0.8
biceps tenotomy	151	28	26	17	0.1
biceps tenodesis	212	39	44	21	0.7
Complications, patient-reported					
delayed wound healing	29	5	8	28	0.4
infection in the wound	19	4	10	53	0.001
frozen shoulder	36	7	19	53	< 0.001
other (various, less frequent)	34	6	6	18	0.5

<sup>a</sup> This does not include patients with fractures less than 2 weeks old. SR: shoulder replacements.

### Assessment of generalizability

To assess generalizability, we compared the patients who were analyzed to the 223 patients who were not available for analysis, but presumably meeting other criteria (they were excluded due to death, missing address, non-response, or missing data). There were no statistically significant differences with regard

Table 3. Risk factors for persistent pain 1–2 years after shoulder replacement. Values are odds ratio (CI)

Variable	All patients, univariate	All patients, multivariate	Fracture, multivariate n = 220	Osteoarthritis, multivariate n = 222
Age	0.98 (0.96–1.00)	0.97 (0.95–0.99)	0.98 (0.95–1.01)	0.94 (0.9–0.99)
Female sex	1.2 (0.8–1.9)	1.3 (0.8–2.2)	1.3 (0.6–2.8)	2.2 (0.9–5.5)
BMI, n = 514	0.95 (0.91–0.99)	0.94 (0.90–0.99)	0.94 (0.88–1.01)	0.94 (0.87–1.01)
Severe pain in first week	4.5 (2.9–6.9)	3.9 (2.4–6.2)	3.6 (1.9–7.0)	4.7 (2.1–10.8)
Pain elsewhere	1.9 (1.2–3.1)	2.0 (1.2–3.5)	2.9 (1.4–5.9)	1.2 (0.4–3.1)
Previous osteosynthesis	4.3 (1.9–9.6)	4.0 (1.7–11)	3.4 (1.3–8.9)	none, not included
Suppl. cuff reconstruction	1.9 (1.1–3.0)	1.6 (0.9–2.8)	1.2 (0.6–2.5)	2.3 (0.6–8.7)
Prosthesis type			too few, not included	
hemi	1 (reference)	1 (reference)		1 (reference)
total	0.18 (0.05–0.60)	0.19 (0.05–0.66)		0.11 (0.02–0.70)
resurfacing	0.57 (0.32–1.03)	0.60 (0.31–1.17)		0.52 (0.19–1.46)
reverse	0.59 (0.35–1.00)	0.83 (0.45–1.50)		1.55 (0.46–5.15)

to age, sex, side operated, previous surgery, hospital volume, or supplementary surgery. Patients who were not available for analysis were more often diagnosed with fracture < 2 weeks old (39%;  $p = 0.01$ ), and less often osteoarthritis (28%;  $p < 0.001$ ) and cuff arthropathy (9%;  $p = 0.03$ ). The type of prosthesis was more often hemiprosthesis (62%;  $p = 0.01$ ) and less often total prosthesis (4%;  $p = 0.01$ ). WOOS and the 2 supplementary questions from the registry tended to be worse, but only 26% of the unavailable patients had completed WOOS.

## Discussion

The prevalence of persistent pain 1–2 years after primary shoulder replacement was 22%, being higher in fracture patients (29%) than in osteoarthritis patients (16%). Comparisons with other studies are complex due to varying definitions and follow-up periods. For hip replacements due to degenerative hip arthritis, 12% of patients experienced pain with moderate, severe, or very severe impact on daily life after 12–18 months (Nikolajsen et al. 2006). For knee replacements mainly due to osteoarthritis, 20% experienced considerable problems with persistent pain (rated 4–5 out of 5) after 14–23 months (Baker et al. 2007). For shoulder replacements, in a review of 40 studies of Neer-II-type shoulder prostheses including 3,584 patients with osteoarthritis mainly, 85% of patients obtained good pain relief while 9% experienced severe pain after 2–12 years (van de Sande et al. 2006). This is comparable to our result of 80% of non-fracture patients reporting pain to be better or much better than before surgery and 10% reporting pain to be worse or much worse. Given the nature of our study, response bias may lead to overestimation of prevalence. However, our generalizability analysis suggested that those who were unavailable for analysis had comparable or worse WOOS, thus supporting the validity of our estimate.

The prevalence of neuropathic pain (as assessed by DN4) was 13%. In a recent article concerning evaluation of failed

shoulder replacement, nerve injury was estimated to occur in 0.6% to 4% of cases (Wiater et al. 2014). Our estimate of neuropathic pain is considerably higher, but it should be considered with caution. DN4 is a screening tool that has not been validated in the Danish language—or in a population of shoulder prosthesis patients.

Chronic or persistent postsurgical pain has been defined as pain that develops after surgery, persists for more than 2 months, and cannot be attributed to causes other than surgery (Macrae and Davies 1999). For certain types of surgery the healing period is longer, and the definition should be adjusted accordingly (Kehlet and Rathmell 2010, Wylde et al. 2013). In the present study, the definition was different, as identification of the underlying causes of persistent pain would require a thorough physical, radiological, neurophysiological, and biochemical examination of each patient. However, this would be necessary to more closely estimate the prevalence of persistent postsurgical pain as defined by Macrae and Davies (1999) and the prevalence of neuropathic pain as defined by the International Association for the Study of Pain (pain caused by a lesion or disease of the somatosensory nervous system). After our study, and in light of the high prevalence of pain found, it would be desirable in further studies to apply the definition of Macrae.

In the present study, complications that may reflect a neuropathic pain state were mentioned and could be investigated further, e.g. complex regional pain syndrome, paralysis of the arm, tight scar tissue, and trapped nerve. Some of the patients experiencing persistent pain would most likely benefit from such an evaluation, including assessment of the possibility of revision or alternative analgesic treatment. A surprisingly high number of the patients used opioids as analgesics (19%), and this also calls for a further assessment of the pain patients. In a review article focusing on complications after 4,010 shoulder replacements, 23% of the patients experienced 1 or more complications within a mean follow-up time of 6 (2–25) years. Many of the complications reported in the review were possibly avoidable or would lead to revision (Gonzalez et al. 2011).

Severe pain in the first postoperative week was associated with a markedly increased risk of persistent pain, although this result may have been influenced by recall bias. The association between acute and chronic postsurgical pain has also been found in other studies. The causal relationship has not been fully established, but the rather high prevalence of 37% of patients experiencing severe pain in the first week identifies a need to treat acute postsurgical pain more aggressively, regardless of the possibility of increased risk of persistent pain. Future intervention studies may determine whether better pain control is attainable, or whether preoperative assessment concerning the risk of severe acute and/or chronic pain could improve patient selection. In osteoarthritis patients, there was a higher risk with hemiprostheses than with total prostheses. This result is in accordance with other studies indicating a superior outcome with a total prosthesis compared to a hemiprosthesis (Bryant et al. 2005, Radnay et al. 2007, Singh et al. 2010, Fevang et al. 2013). As in all registry studies, a limitation exists in the completeness and reliability of registry data such as prosthesis type and supplementary surgery, and this problem is not easy to quantify. Also, the questionnaire developed did not undergo testing of reliability and validity beyond the method described.

In conclusion, persistent pain after shoulder replacement is a daily burden to many patients. Further prospective studies are required to confirm our results and to evaluate the causes of persistent pain and the treatments or preventive measures required. Studies should not only concentrate on prosthesis selection and surgical complications, but also involve (1) preoperative assessment to effectively improve patient selection, and (2) improvement of postoperative pain management and its effect on the development of persistent pain.

### Supplementary data

The Questionnaire is available at [www.actaorthop.org](http://www.actaorthop.org), identification number 7739.

LN came up with the idea. KTB collected the data and, assisted by BB, performed the analysis. All the authors contributed to study design, interpretation, and critical revision of the manuscript. The final manuscript was approved by all the authors.

We thank Gerhardt Teichert and Janne Ovesen for contributing to the interpretation of data and for commenting on the manuscript, and secretary Line Jensen for proofreading the manuscript. This work was supported by the Health Research Fund of Central Denmark Region, the Hede Nielsen Family Foundation, and the Augustinus Foundation.

No competing interests declared.

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Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

## Spørgeskema i forbindelse med smertebehandling ved skulderprotese

Kære Patient,

Du bedes udfylde spørgeskemaet med kuglepen til de anførte tidspunkter, så godt du kan, og gøre eventuelle rettelser tydelige. Du er velkommen til at spørge personalet eller ringe til projektleder Karen Toftdahl Bjørnholdt på tlf. 25 54 45 47 alle dage mellem kl. 8 og 21 hvis du er i tvivl. På forhånd mange tak for hjælpen!

Før operationen:

Hvordan var niveauet af smerter i skulderen før operationen, når skulderen var i <b>hvile</b> ?											
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
	0	1	2	3	4	5	6	7	8	9	10
Hvordan var niveauet af smerter i skulderen før operationen, når skulderen var i <b>aktivitet</b> ?											
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
	0	1	2	3	4	5	6	7	8	9	10
Hvad brugte du af <b>smertestillende</b> midler før operationen?											
Navn	Styrke (mg)		Antal pr. gang		Hvor ofte?						

På operationsdagen, udfyldes til de angivne tidspunkter:

Hvornår var operationen slut? Spørg eventuelt personalet.		Klokken _____:_____									
<b>Da du vågner</b> efter operationen: Hvordan er niveauet af smerter i skulderen nu?											
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
	0	1	2	3	4	5	6	7	8	9	10
<b>Efter 2 timer</b> , dvs. kl. _____: : Hvordan er niveauet af smerter i skulderen nu?											
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
	0	1	2	3	4	5	6	7	8	9	10
<b>Efter 4 timer</b> , dvs. kl. _____: : Hvordan er niveauet af smerter i skulderen nu?											
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
	0	1	2	3	4	5	6	7	8	9	10

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

**Efter 8 timer**, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter             Værst tænkelige smerter  
0 1 2 3 4 5 6 7 8 9 10

Hvad brugte du af **smertestillende** midler på operationsdagen? *Skriv ned efterhånden.*

Klokkeslæt	Navn	Styrke (mg)	Antal

Dagen efter operationen:

Hvordan var niveauet af smerter **om natten, når det var højest**? *Udfyldes om morgenen.*

Ingen smerter             Værst tænkelige smerter  
0 1 2 3 4 5 6 7 8 9 10

**Efter 24 timer**, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter             Værst tænkelige smerter  
0 1 2 3 4 5 6 7 8 9 10

**Efter 32 timer**, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter             Værst tænkelige smerter  
0 1 2 3 4 5 6 7 8 9 10

Hvad brugte du af **smertestillende** midler dagen efter operationen? *Skriv ned efterhånden.*

Klokkeslæt	Navn	Styrke (mg)	Antal

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

## Anden dag efter operationen:

Hvordan var niveauet af smerter **om natten, når det var højest?** Udfyldes om morgenen.

Ingen smerter            Værst tænkelige smerter

0 1 2 3 4 5 6 7 8 9 10

Efter 48 timer, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter            Værst tænkelige smerter

0 1 2 3 4 5 6 7 8 9 10

Efter 56 timer, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter            Værst tænkelige smerter

0 1 2 3 4 5 6 7 8 9 10

Hvad brugte du af **smertestillende** midler anden dag efter operationen? *Skriv ned efterhånden.*

Klokkeslæt	Navn	Styrke (mg)	Antal

## Tredje dag efter operationen:

Hvordan var niveauet af smerter **om natten, når det var højest?** Udfyldes om morgenen.

Ingen smerter            Værst tænkelige smerter

0 1 2 3 4 5 6 7 8 9 10

Efter 72 timer, dvs. kl. \_\_\_\_\_: Hvordan er niveauet af smerter i skulderen nu?

Ingen smerter            Værst tænkelige smerter

0 1 2 3 4 5 6 7 8 9 10

Hvad brugte du af **smertestillende** midler tredje dag efter operationen? *Skriv ned efterhånden.*

Klokkeslæt	Navn	Styrke (mg)	Antal

Fortsættes på næste side

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

Klokkeslæt	Navn	Styrke (mg)	Antal

Har du oplevet bivirkninger i form af...

	Nej	Ja, lidt	Ja, meget
Kvalme	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Opkastning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Træthed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Forstoppelse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mavesmerter/utilpashed i maven	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hæshed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Åndenød	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hængende øjenlåg på den opererede side	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kraftsløshed i den opererede arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Snurren eller prikken i den opererede arm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sivning fra såret	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andet:			

Hvis du før operationen havde vidst, at det ville forløbe, som det rent faktisk gjorde, ville du så stadig have valgt at gennemgå operationen? *Sæt en cirkel om tallet.*

Ja.....1  
Nej.....2

Har du nogen kommentarer til forløbet?

Mange tak for din deltagelse i undersøgelsen. Spørgeskemaet indsendes i medfølgende svarkuvert til projektlederen (på Regionshospitalet Horsens) eller afleveres til personalet.

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

## Spørgeskema i forbindelse med smertebehandling ved skulderoperation

Kære Patient,

Du bedes udfylde spørgeskemaet med kuglepen. Ved rettelser skal du strege ud – men holde det oprindelige læseligt, og gøre det nye svar ekstra tydeligt.

Smerter er svære at måle, og du vil blive bedt om at angive dine gennemsnitlige smerter, hvilket heller ikke er særlig nemt. Alligevel beder vi dig om at udfylde alle felter, så godt du nu kan.

Når skemaet er færdigt, sendes det til sygehuset i vedlagte svarkuvert. Du vil efterfølgende blive ringet op, hvis der er uklarheder, så vi kan få alle svarene samlet rigtigt ind.

Du er meget velkommen til at spørge personalet eller ringe til projektleder Karen Toftdahl Bjørnholdt på tlf. 25 54 45 47 alle dage mellem kl. 8 og 21, hvis du er i tvivl.

På forhånd mange tak for hjælpen!

### Før operationen:

Hvordan var skuldersmerterne før operationen, når skulderen var i <b>hvile</b> ?												
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter										
	0	1	2	3	4	5	6	7	8	9	10	
Hvordan var skuldersmerterne før operationen, når skulderen var i <b>aktivitet</b> ?												
Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter										
	0	1	2	3	4	5	6	7	8	9	10	
Hvad brugte du af <b>smertestillende</b> midler før operationen?												
Navn	Styrke (mg)			Antal pr. gang			Hvor ofte?					

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

## På operationsdagen:

Udfyldes på sygehuset	Hvornår var operationen slut? Spørg eventuelt personalet. Klokken _____:		
	<b>Da du vågner</b> efter operationen: Hvordan er skuldersmerterne nu?		
	Ingen smerter <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10 Værst tænkelige smerter		
Udfyldes på sygehuset	<b>Lige før du forlader sygehuset</b> , kl. _____: Hvordan er skuldersmerterne nu?		
	Ingen smerter <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10 Værst tænkelige smerter		
	Hvad brugte du af <b>smertestillende</b> midler på operationsdagen, fra du forlod sygehuset og til kl. 24? <i>Skriv ned efterhånden.</i>		
Klokkeslæt	Navn	Styrke (mg)	Antal
Udfyldes efter hjemkomsten	<b>Efter 8 timer</b> , dvs. kl. _____: Hvordan er skuldersmerterne nu?		
	Ingen smerter <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10 Værst tænkelige smerter		
	Hvordan var skuldersmerterne <b>på operationsdagen</b> , efter du forlod sygehuset, <b>da de var værst?</b>		
	Ingen smerter <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10 Værst tænkelige smerter		
Udfyldes efter hjemkomsten	Hvordan var skuldersmerterne <b>på operationsdagen</b> , efter du forlod sygehuset, <b>i gennemsnit?</b>		
	Ingen smerter <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10 Værst tænkelige smerter		

## Dagen efter operationen:

Udfyldes om morgenen, kl. 8	Dagen efter operationen, <b>ca. kl. 8</b> : Hvordan er skuldersmerterne nu?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Udfyldes om aftenen, kl. 20	Hvordan var skuldersmerterne den <b>første nat, da de var værst</b> ?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Hvordan var skuldersmerterne den <b>første nat, i gennemsnit</b> ?												
Ingen smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Værst tænkelige smerter
	0	1	2	3	4	5	6	7	8	9	10	
Hvad brugte du af <b>smertestillende</b> midler dagen efter operationen fra kl. 00 til kl. 24? <i>Skriv ned efterhånden.</i>												
Klokkeslæt	Navn						Styrke (mg)			Antal		
Udfyldes om aftenen, kl. 20	Dagen efter operationen <b>kl. ca. 20</b> : Hvordan er skuldersmerterne nu?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Udfyldes om aftenen, kl. 20	Hvordan var skuldersmerterne dagen efter operationen, <b>da de var værst</b> ?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Udfyldes om aftenen, kl. 20	Hvordan var skuldersmerterne dagen efter operationen, <b>i gennemsnit</b> ?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_

## Anden dag efter operationen:

Udfyldes om morgenen, kl. 8	Anden dag efter operationen, <b>ca. kl. 8</b> : Hvordan er skuldersmerterne nu?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Udfyldes om aftenen, kl. 20	Anden dag efter operationen <b>kl. ca. 20</b> : Hvordan er skuldersmerterne nu?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Hvordan var skuldersmerterne den <b>anden nat, da de var værst</b> ?												
Ingen smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Værst tænkelige smerter
	0	1	2	3	4	5	6	7	8	9	10	
Hvordan var skuldersmerterne den <b>anden nat, i gennemsnit</b> ?												
Ingen smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Værst tænkelige smerter
	0	1	2	3	4	5	6	7	8	9	10	
Hvad brugte du af <b>smertestillende</b> midler den anden dag efter operationen fra kl. 00 til kl. 24? <i>Skriv ned efterhånden.</i>												
Klokkeslæt	Navn		Styrke (mg)		Antal							

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

Tredje dag efter operationen:

Udfyldes om morgenen, kl. 8	Tredje dag efter operationen, <b>ca. kl. 8</b> : Hvordan er skuldersmerterne nu?											
	Ingen smerter	<input type="checkbox"/>	Værst tænkelige smerter									
		0	1	2	3	4	5	6	7	8	9	10
Hvordan var skuldersmerterne den <b>tredje nat, da de var værst</b> ?												
Ingen smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Værst tænkelige smerter
	0	1	2	3	4	5	6	7	8	9	10	
Hvordan var skuldersmerterne den <b>tredje nat, i gennemsnit</b> ?												
Ingen smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Værst tænkelige smerter
	0	1	2	3	4	5	6	7	8	9	10	
Hvad brugte du af <b>smertestillende</b> midler den tredje dag efter operationen fra kl. 00 til kl. 24? <i>Skriv ned efterhånden.</i>												
Klokkeslæt	Navn						Styrke (mg)			Antal		

Har du oplevet bivirkninger i form af...

	Nej	Ja, lidt	Ja, meget
Kvalme	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Træthed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Opstemthed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nedtrykthed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mavesmerter/ubehag i maven	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Søvnbesvær pga. smerter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Søvnbesvær i det hele taget	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blå mærker på den opererede skulder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Svimmelhed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Forstoppelse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andet:			

Patient nr.: \_\_\_\_\_

Operationsdato: \_\_\_\_/\_\_\_\_/201\_\_\_\_

**Hvis du før operationen havde vidst, at det ville forløbe, som det rent faktisk gjorde, ville du så stadig have valgt at gennemgå operationen? Sæt en cirkel om tallet**

Ja.....1

Nej.....2

**Hvilken behandling tror du, at du fik? Sæt en cirkel om tallet**

Placebo, inaktiv behandling.....1

Aktiv behandling

    Dexamethason 8 mg, dvs. vanlig behandling.....2

    Dexamethason 40 mg, dvs. højere dosis end vanligt.....3

    Dexamethason, ved ikke om det var 8 eller 40 mg.....4

Ved ikke.....5

**Har du nogle kommentarer til forløbet?**

# Questionnaire

It is very important that you answer all of the questions that are relevant to you as best you can. Use a blue or black pen. If you are unable to answer, please write the reason in the box with the question.

All questions are related to the shoulder where you have your prosthesis, unless otherwise noted.

Check the box next to the most accurate answer, as shown in this example:

*Did you experience pain after the surgery?*

Yes.....<sub>1</sub>

No..... <sub>2</sub>

Don't know..... <sub>3</sub>

*(Do not worry about the numbers by the boxes; they will be used later when the data is registered)*

First, some questions about pain before and immediately after the surgery

1. Date of completing this form: \_\_\_\_\_ / \_\_\_\_\_ / 2013

2. Did you experience any pain in your shoulder before the shoulder replacement surgery?

Yes, for more than 6 months..... <sub>1</sub>

Yes, for 1-6 months ..... <sub>2</sub>

Yes, for less than a month..... <sub>3</sub>

No, no pain before the surgery..... <sub>4</sub> *If your answer is no, please go to question 4*

3. On average, how much pain did you experience in the week before the surgery?

No pain ..... <sub>1</sub>

Mild pain ..... <sub>2</sub>

Moderate pain..... <sub>3</sub>

Severe pain ..... <sub>4</sub>

4. On average, how much pain did you experience in the first week after the surgery?

No pain ..... <sub>1</sub>

Mild pain ..... <sub>2</sub>

Moderate pain ..... <sub>3</sub>

Severe pain ..... <sub>4</sub>

5. For how long after the surgery did you experience pain?

Less than 3 months ..... <sub>1</sub>

For 3-6 months ..... <sub>2</sub>

Over 6 months ..... <sub>3</sub>

I still experience pain ..... <sub>4</sub>

6. After the surgery, have you experienced problems with one or more of the following symptoms?

	Yes	No
Healing of the wound.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>
Infection in the wound.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>
Broken arm/shoulder.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>
Phlebitis/embolism in the arm .....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>
Frozen shoulder.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>
Other symptoms:_____		

7. Have you had additional surgery in your shoulder after you got your shoulder prosthesis?

Yes..... <sub>1</sub> What kind of surgery?\_\_\_\_\_

. Date:\_\_\_\_\_

No..... <sub>2</sub>

All of the following questions concern how you feel now:

8. During the last month, have you experienced pain in the shoulder with the prosthesis?

Yes, constantly..... <sub>1</sub>

Yes, every day but not all the time..... <sub>2</sub>

Yes, but not every day .....

No, no pain during the last month..... <sub>4</sub> *If no, please go to question 15*

9. On average, how much pain have you experienced in your shoulder in the last month? (*mark your answer by checking one of the boxes below*)

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable
	<input type="checkbox"/>											

10. During the last month, how severe has the worst pain in your shoulder been? (*mark your answer by checking one of the boxes below*)

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable
	<input type="checkbox"/>											

11. Overall, how much does the pain bother you in your everyday life?

Not at all..... <sub>1</sub>

A little..... <sub>2</sub>

Somewhat..... <sub>3</sub>

Much..... <sub>4</sub>

Very much..... <sub>5</sub>

12. Compared to before the operation, how is your shoulder now regarding pain?

- Much better..... <sub>1</sub>  
 Better..... <sub>2</sub>  
 The same..... <sub>3</sub>  
 Worse..... <sub>4</sub>  
 A lot worse..... <sub>5</sub>

13. Does the pain have one or more of the following characteristics?

- |                      | Yes                                   | No                                    |
|----------------------|---------------------------------------|---------------------------------------|
| Burning.....         | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |
| Painful cold.....    | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |
| Electric shocks..... | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |

14. Is the pain associated with one or more of the following symptoms in the same area?

- |                       | Yes                                   | No                                    |
|-----------------------|---------------------------------------|---------------------------------------|
| Tingling.....         | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |
| Pins and needles..... | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |
| Numbness.....         | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |
| Itching.....          | <input type="checkbox"/> <sub>1</sub> | <input type="checkbox"/> <sub>2</sub> |

15. Have you experienced reduced sensation when you touch the area with something soft (e.g. a piece of cotton)?

- Yes..... <sub>1</sub>  
 No..... <sub>2</sub>

16. Have you experienced reduced sensation when you touch the area with something sharp/pointy? (e.g. a toothpick)?

- Yes..... <sub>1</sub>  
 No..... <sub>2</sub>

17. In the painful area, can the pain be caused or increased by brushing with something soft?

- Yes..... <sub>1</sub>  
 No..... <sub>2</sub>

18. Do you experience pain other places in your body besides your shoulder?

- No..... <sub>1</sub>  
 Yes, mild pain <sub>2</sub>  
 Yes, moderate pain <sub>3</sub>  
 Yes, severe pain <sub>4</sub>
- } If yes, where: \_\_\_\_\_

19. Do you take any pain medication on a daily basis? (mark your answer by checking one of the boxes below)

No..... <sub>1</sub>

Yes, for pain in the shoulder..... <sub>2</sub>

Yes, for pain elsewhere..... <sub>3</sub>

Yes, for pain in the shoulder as <sub>4</sub>

well as elsewhere

} Name(s) of daily  
medication: \_\_\_\_\_

\_\_\_\_\_

20. Do you take any pain medication, which you do not take on a daily basis? (mark your answer by checking one of the boxes below)

No <sub>1</sub>

Yes, for pain in the shoulder..... <sub>2</sub>

Yes, for pain elsewhere..... <sub>3</sub>

Yes, for pain in the shoulder as <sub>4</sub>

well as elsewhere

} Name(s) of daily  
medication: \_\_\_\_\_

\_\_\_\_\_

21. Do you use other forms of pain relieving treatments?

	No	Acupuncture	Physiotherapy	Chiropractor	Hydrotherapy
For pain in the shoulder?.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
For pain elsewhere?.....	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>
For pain in both the shoulder and elsewhere?...	<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

Other pain relieving treatments: \_\_\_\_\_

22. Please note your height and your weight

Height: \_\_\_\_\_ cm

Weight: \_\_\_\_\_ kg

23. Other comments?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

24. May we contact you again by phone or email if we need to follow up on your answers?

Yes..... <sub>1</sub>

No..... <sub>2</sub>

Phone: \_\_\_\_\_ Email: \_\_\_\_\_

**Thank you very much!**

## THESES FROM THE ORTHOPAEDIC RESEARCH GROUP

*Doctoral and PhD Theses from the Orthopaedic Research Group, [www.OrthoResearch.dk](http://www.OrthoResearch.dk), Aarhus University Hospital, Denmark*

### **Doctoral Theses**

1. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs  
Kjeld Søballe, 1993  
*Acta Orthop Scand (Suppl 255) 1993;54*
2. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation  
Martin Lind, October 1998  
*Acta Orthop Scand (Suppl 283) 1998;69*
3. Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods  
Søren Overgaard, 2000  
*Acta Orthop Scand (Suppl 297) 2000;71*
4. Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology  
Steffen Jacobsen, December 2006  
*Acta Orthopaedica (Suppl 324) 2006;77*
5. Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing  
Michael Ulrich-Vinther, March 2007  
*Acta Orthopaedica (Suppl 325) 2007;78*
6. Assessment of adult hip dysplasia and the outcome of surgical treatment  
Anders Troelsen, February 2012  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*

### **PhD Theses**

7. In vivo and vitro stimulation of bone formation with local growth factors  
Martin Lind, January 1996  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*
8. Gene delivery to articular cartilage  
Michael Ulrich-Vinther, September 2002  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*
9. The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles  
Ole Rahbek, October 2002  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*
10. Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques  
Søren Kold, January 2003  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*
11. Stimulation and substitution of bone allograft around non-cemented implants  
Thomas Bo Jensen, October 2003  
*[www.OrthoResearch.dk](http://www.OrthoResearch.dk)*

12. The influence of RGD peptide surface modification on the fixation of orthopaedic implants  
Brian Elmengaard, December 2004  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
13. Biological response to wear debris after total hip arthroplasty using different bearing materials  
Marianne Nygaard, June 2005  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
14. DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups  
Mogens Berg Laursen, November 2005  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
15. Studies based on the Danish Hip Arthroplasty Registry  
Alma B. Pedersen, 2006  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
16. Reaming procedure and migration of the uncemented acetabular component in total hip replacement  
Thomas Baad-Hansen, February 2007  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
17. On the longevity of cemented hip prosthesis and the influence on implant design  
Mette Ørskov Sjøland, April 2007  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
18. Combination of TGF- $\beta$ 1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo  
Anders Lamberg, June 2007  
[www.OrthoResearch.dk](http://www.OrthoResearch.dk)
19. Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration  
Inger Mechlenburg, August 2007  
*Acta Orthopaedica (Suppl 329) 2008;79*
20. Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status  
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