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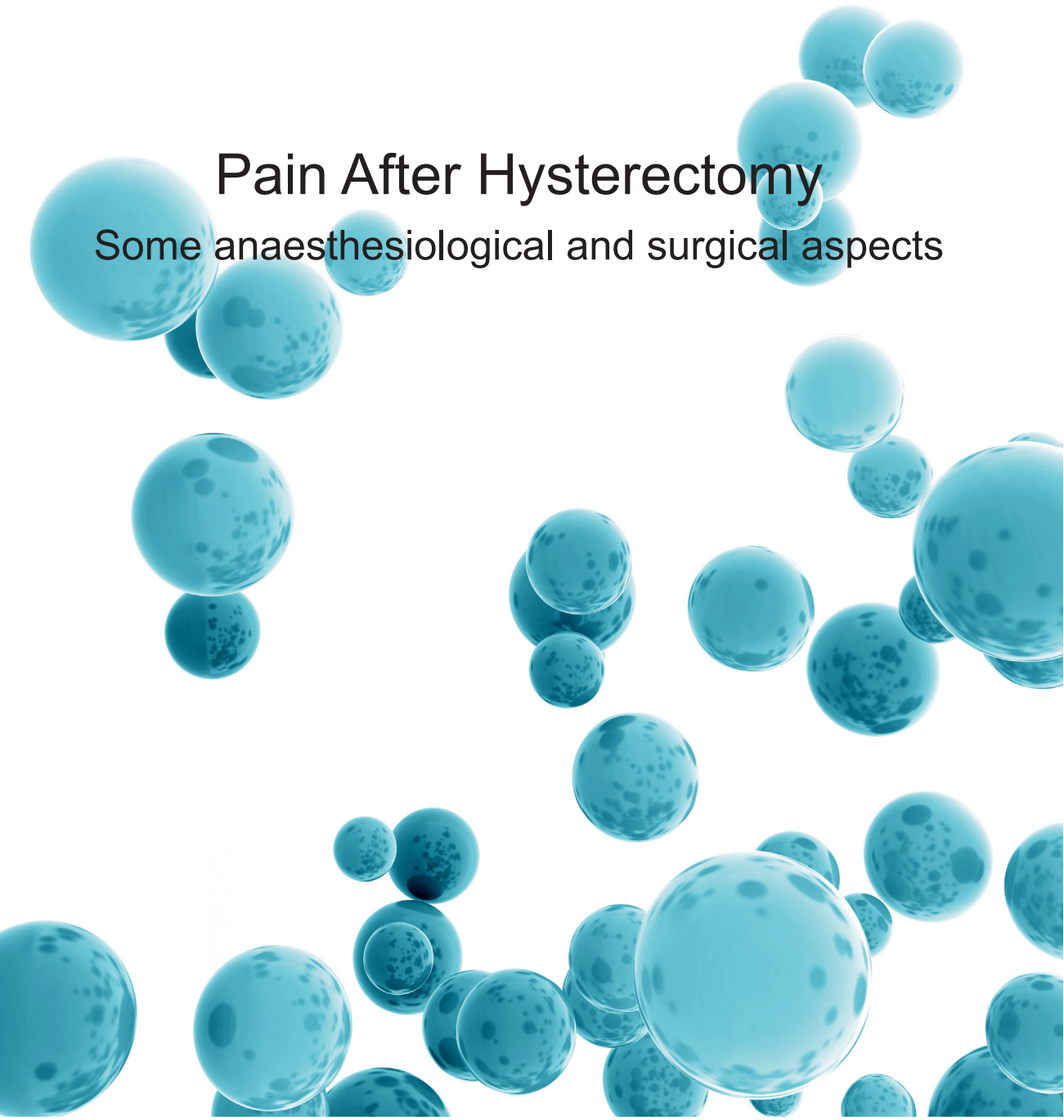
Pain After Hysterectomy

Some anaesthesiological and surgical aspects



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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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University of Tampere, School of Medicine
Tampere University Hospital, Department of Anaesthesia
Valkeakoski Regional Hospital
Finland

Supervised by
Professor Arvi Yli-Hankala
University of Tampere
Finland
MD, PhD Maija-Liisa Kalliomäki
University of Tampere
Finland

Reviewed by
Docent Päivi Härkki
University of Helsinki
Finland
Docent Timo Salomäki
University of Oulu
Finland

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To Terhi, Mari and Markku

ABSTRACT

Postoperative pain is one of the most significant factors that impact on the patient´s recovery from surgery. Despite many advances in pain management it remains a challenge to achieve the appropriate treatment for every surgical patient. Many factors affect the severity of acute pain. It remains unresolved whether the choice of anaesthetic has any significance on the severity of postoperative pain. How different approaches to hysterectomy affect the pain experienced likewise remains unknown. Severe acute postsurgical pain is a risk factor for persistent pain. A surgical technique entailing a great risk of nerve damage is another of the significant predictors of persistent postsurgical pain. However, very little is known about the specific predictors and characteristics of persistent pain after hysterectomy.

The aim of this thesis was to study whether the choice of anaesthetic, i.e. propofol or sevoflurane, or the choice of surgical technique (vaginal or laparoscopic), has any impact on acute postoperative pain. The aims were also to ascertain the prevalence of persistent postsurgical pain after vaginal or laparoscopic hysterectomy, the characteristics of persistent pain after hysterectomy, predictors for persistent pain, and the impact of pain on patients´ health related quality of life.

In Study I, the consumption of oxycodone among 148 women undergoing laparoscopic hysterectomy with or without salpingo-oophorectomy for benign conditions was measured for 20 postoperative hours. The patients were randomly assigned to receive either sevoflurane or propofol as their main anaesthetic during surgery. The patients were blinded in regard to the anaesthetic. The primary endpoint was the cumulative consumption of oxycodone. The secondary endpoints were the severity of pain, nausea and state of sedation.

Study II included women undergoing hysterectomy with or without salpingo-oophorectomy for non-malignant reasons. Vaginal and laparoscopic surgical procedures were used in 90 and 74 patients respectively. The main indication in both groups was uterine leiomyomas. General anaesthesia was used in all cases. The anaesthesia protocol was the same as in the propofol group in Study I. The primary endpoint was the cumulative consumption of oxycodone in 20

postoperative hours. The secondary endpoints were severity of pain, duration of surgery, length of hospital stay and blood loss.

In Study III, the prevalence of persistent postsurgical pain six months after hysterectomy was evaluated using a questionnaire sent to the 242 patients of Studies I and II. The final study population consisted of 227 respondents. Questions about the severity and characteristics of persistent pelvic pain, sleeping disorders and the effect of pain on daily activities were included.

In Study IV clinical examinations were performed on 16 women who had participated in Study III and suffered persistent pelvic pain for over six months after hysterectomy. The patients were also asked to complete the SF-36 generic health status measure.

The choice of anaesthetic, sevoflurane or propofol, for the maintenance of anaesthesia had no impact on the amount of oxycodone consumed, or on the severity of pain as rated by pain scores in the acute phase period after hysterectomy. The pain was more severe one hour after vaginal hysterectomy than after laparoscopic hysterectomy. Thereafter the need for oxycodone was greater after vaginal hysterectomy than after laparoscopic hysterectomy although the difference was significant only four and six hours after surgery. The prevalence of persistent pelvic pain six months after hysterectomy was 26%. Pain was rated mild by most of the patients and severe by four (6.9%) of the 58 patients. In a multivariable analysis, smoking, severity of acute postoperative pain and laparoscopic procedure were associated with persistent pain after hysterectomy. The persistent pelvic pain after hysterectomy was regarded as pain mostly caused by surgery and was neuropathic in nature in over half of the patients. The women suffering from persistent pain after hysterectomy had impaired health related quality of life compared with the Finnish general female cohort of 1,133 women.

In summary, anaesthetic seems to have no clinical significant effect on the severity of pain. Postoperative acute pain seems to be less severe after laparoscopic hysterectomy than after vaginal hysterectomy. Persistent postsurgical pain is common after hysterectomy, the underlying mechanisms appear to be variable and smoking is the strongest predictor for pain. Although persistent pain interferes little with daily activities it has an impact on the health related quality of life.

TIIVISTELMÄ

Leikkauksen jälkeinen kipu on yksi tärkeimpiä potilaan leikkauksesta toipumiseen vaikuttavia tekijöitä. Vaikka kivun hoito on kehittynyt, osa potilaista kärsii edelleen leikkauksen jälkeisestä kivusta. Tiedetään, että monet eri tekijät vaikuttavat akuutin kivun voimakkuuteen. Ei kuitenkaan ole selvää, onko nukutusaineen valinnalla merkitystä leikkauksen jälkeisen kivun voimakkuuteen. Ei myöskään tiedetä, mikä merkitys kohdunpoiston eri leikkaustekniikoilla on potilaan kokemaan kipuun.. Kova akuutti leikkauksen jälkeinen kipu on pitkittyneen kivun riskitekijä. Myös leikkaustekniikka, jonka käyttöön liittyy suuri hermovaurioriski, lisää kivun pitkittymisen mahdollisuutta. Kovin paljon ei tiedetä pitkittyneen kivun riskitekijöistä eikä myöskään pitkittyneen kivun luonteesta kohdun poiston jälkeen.

Tämän väitöstyön ensimmäinen tavoite oli selvittää, onko nukutusaineen valinnalla propofolin tai sevofluraanin kesken merkitystä akuuttiin leikkauksen jälkeiseen kipuun. Toisena tavoitteena oli selvittää, onko leikkaustekniikoilla tähystysleikkaus tai emättimen kautta tapahtuva kohdun poisto vaikutusta kivun voimakkuuteen. Tavoitteena oli myös selvittää pitkittyneen kivun esiintyvyyttä tähystysleikkauksena tehtävän tai emättimen kautta tehtävän kohdunpoiston jälkeen, selvittää pitkittyneen kivun luonnetta, ennustekijöitä kivun pitkittymiselle ja kivun merkitystä potilaiden elämänlaatuun.

Ensimmäisessä osatyössä mitattiin oksikodonin kulutusta tähystyksenä tehtävän kohdunpoiston jälkeen 20 tunnin ajalta. Tutkimukseen osallistui 148 naista, joille tehtiin kohdunpoisto hyvänlaatuisista syistä. Potilaat satunnaistettiin nukutusaineen suhteen kahteen ryhmään, propofoli- ja sevofluraaniryhmään. Kaikki potilaat sokkoistettiin käytetyn nukutusaineen suhteen. Päämuuttuja tässä tutkimuksessa oli kivun hoitoon annetun oksikodonin kumulatiivinen määrä 20 tuntia leikkauksen jälkeen. Muita muuttujia olivat kivun voimakkuus, pahoinvointi ja sedaation aste.

Toisessa osatyössä tutkittiin kipulääkkeen tarvetta kohdunpoistoleikkauksen jälkeen. 90 naiselle tehtiin kohdunpoistoleikkaus emättimen kautta, ja 74 naiselle kohdunpoisto tehtiin tähystysleikkauksena. Kaikki leikkaukset tehtiin hyvänlaatuisista syistä. Tavallisin syy kohdunpoistolle oli hyvänlaatuinen kohdun lihaskasvain eli myooma. Molempien ryhmien hoidossa käytettiin yleisanestesiaa. Tässä tutkimuksessa anestesiat olivat samanlaisia kuin ensimmäisen osatyön

profoliryhmän potilaiden anestesiat. Päämuuttuja oli oksikodonin kumulatiivinen kulutus 20 tuntia leikkauksen jälkeen. Muita muuttujia olivat kivun voimakkuus, leikkauksen kesto, sairaalajakson pituus ja veren hukka.

Kolmannessa osatyössä selvitettiin pitkittyneen kivun esiintyvyyttä kuusi kuukautta leikkauksen jälkeen. Osatöihin 1 ja 2 osallistuneille 242 potilaalle lähetettiin kirjekysely. Kyselyyn vastasi 227 potilasta. Kirjekysely sisälsi kysymyksiä pitkittyneen kivun voimakkuudesta ja kivun luonteesta, univaikeuksista ja kivun vaikutuksesta päivittäiseen toimintakykyyn.

Neljännessä osatyössä 16 potilaalle tehtiin kliininen tutkimus. Nämä potilaat olivat osallistuneet osatyö kolmeen ja he olivat kärsineet pitkittyneestä kivusta vähintään kuuden kuukauden ajan kohdunpoistonsa jälkeen. Potilaat myös täyttivät SF-36 elämänlaatua selvittävän kyselyn.

Anestesian ylläpitoaineen valinnalla sevofluraanin tai propofolin välillä ei ollut mitään merkitystä oksikodonin kulutukseen eikä kivun voimakkuuteen ensimmäisen 20 tunnin aikana kohdunpoiston jälkeen. Emättimen kautta tehtävän kohdunpoiston jälkeen oksikodonin kulutus oli isompaa kuin tähystysleikkauksen jälkeen; ero oli merkitsevä neljä ja kuusi tuntia leikkauksen jälkeen. Pitkittynyttä lantion alueen kipua esiintyi 26 %:lla potilaista. Suurimmalla osalla potilaista kipu oli lievää. Neljä potilasta 58:sta (6.9 %) kärsi kovasta kivusta. Monimuuttuja-analyysi osoitti, että pitkittynyt kipu oli yhteydessä tupakointiin, akuuttiin leikkauksen jälkeiseen kipuun ja tähystystoimenpiteeseen. Pitkittynyt lantion alueen kipu oli luonteeltaan neuropaattista yli puolella potilaista ja kivun syynä arvioitiin olevan pääsääntöisesti edeltävä kohdunpoisto. Pitkittyneestä kohdunpoistoleikkauksen jälkeisestä kärsivien naisten elämänlaatu oli alentunut verrattuna 1133 naista käsittävään suomalaisten naisten kohorttiin.

Yhteenvetona voidaan todeta, että nukutusaineen valinnalla ei näyttäisi olevan kliinistä merkitystä leikkauksen jälkeisen kivun voimakkuuteen. Leikkauksen jälkeinen akuutti kipu vaikuttaisi olevan vähäisempää tähystystoimenpiteen jälkeen kuin emättimen kautta tehtävän kohdunpoiston jälkeen. Pitkittynyt leikkauksen jälkeinen kipu on yleistä kohdunpoiston jälkeen, kivun syyt näyttäisivät olevan vaihtelevia ja tupakointi on vahvin ennustekijä kivun pitkittymiselle. Vaikka pitkittynyt kipu vaikuttaa vain vähän päivittäiseen toimintakykyyn, kivulla on merkitystä elämänlaadun kannalta.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, referred to in the text by their Roman numerals (I-IV):

I Pokkinen SM, Yli-Hankala A, Kalliomäki ML. The effects of propofol vs. sevoflurane on post-operative pain and need of opioid. Acta Anaesthesiol Scand 2014; 58: 980-985.

II Pokkinen SM, Kalliomäki ML, Yli-Hankala A, Nieminen K. Less postoperative pain after laparoscopic hysterectomy than after vaginal hysterectomy. Arch Gynecol Obstet 2015; 292: 149-154

III Pokkinen SM, Nieminen K, Yli-Hankala A, Kalliomäki ML. Persistent post-hysterectomy pain. A prospective, observational study. Eur J Anaesthesiol 2015; 32: 718-724

IV Pokkinen SM, Nieminen K, Yli-Hankala A, Kalliomäki ML. Characterization of persistent pain after hysterectomy based on gynaecological and sensory examination. Scand J Pain 2016; 11: 42-48

ABBREVIATIONS

AMPA	Alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
ATP	Adenosine-5´-triphospate
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
DN4	Douleur Neuropathique 4 Questions
EFNS	European Federation of Neurological Societies
GABA	Gamma-aminobutyric acid
H+	Protons
HRQoL	Health related quality of life
IASP	International association for the Study of Pain
IV	Intravenous
LAVH	Laparoscopically assisted vaginal hysterectomy
LH	Laparoscopic hysterectomy
MPQ	McGill Pain Questionnaire
NeuPSIG	Neuropathic Pain Special Interest Group
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NRS	Numeric rating scale
OIH	Opioid induced hyperalgesia
OR	Odds ratio
PACU	Postanaesthesia care unit
PAG	Periaqueductal grey
PCA	Patient controlled analgesia
PPSP	Persistent postsurgical pain
Q_1	Lower quartile
Q_3	Upper quartile
RVM	Rostroventral medulla
SD	Standard deviation

SF-36	Short form -36
TCI	Target controlled infusion
TIVA	Total intravenous anaesthesia
TLH	Total laparoscopic hysterectomy
TNF-α	Tumour necrosis factor-alpha
TRP	Transient receptor potential
TRPA1	Transient receptor potential A1
TRPV1	Transient receptor potential V1
VAS	Visual analogue scale
VH	Vaginal hysterectomy

CONTENTS

1 INTRODUCTION

Despite advances in pain research, many patients still have to suffer from postoperative pain. Severe acute pain is considered one of the known predictors for persistent postsurgical pain. Another significant risk factor is a surgical approach with a risk of causing nerve damage (Perkins and Kehlet 2000; Peters et al. 2007; McGreevy et al. 2011; Schug and Pogatzki-Zahn 2011). Hysterectomy is one of the most frequent surgical procedures for benign conditions. In Finland 6700 hysterectomies are performed annually (Brummer et al. 2009; Kovac 2014).

The properties of anaesthetics differ in their tendency to induce postoperative nausea and prolonged sedation (Visser et al. 2001; White 2008). Effect of anaesthetics on the severity of postsurgical pain is unclear (White 2010). Mini-invasive technique has been shown to reduce the intensity of postoperative pain. This has also been shown after vaginal or laparoscopic hysterectomy, compared to an abdominal approach (Garry et al. 2004; Schindlbeck et al. 2008; Gerbershagen et al. 2013). Many earlier studies have compared vaginal and laparoscopic techniques in hysterectomy, but the main interests for these studies have been the prevalence of surgical complications, duration of surgery and of hospital stay. The laparoscopic approach has become common only in recent years; thus little is known so far about acute and persistent postsurgical pain after laparoscopic hysterectomy (Soriano et al. 2001; Brandsborg et al. 2009; Gendy et al. 2011; Sesti et al. 2014).

This thesis focuses on acute and persistent pain after hysterectomy. The aim was to ascertain whether the choice of anaesthetic or the surgical technique of hysterectomy have any impact on the severity of acute pain. Other aims were to establish the prevalence and intensity of persistent pain after hysterectomy and possible predictors for persistent pain, and to clarify the characteristics of pain and its consequences for women´s health related quality of life.

2 REVIEW OF THE LITERATURE

According to the International Association for the Study of Pain (IASP) pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". The mere activity in nociceptive pathways is not pain; pain is always a psychological state (Mersky and Bogduk 1994).

2.1 Pathophysiology of postoperative pain

The mechanism of acute postoperative pain differs from those of other acute pain conditions; e.g. rheumatoid arthritis or acute herpes zoster (Brennan 2011). The tissue injury caused by surgery triggers a cascade of events in order to reject infection, limit further injury and start repair (Voscopoulos and Lema 2010).

2.1.1 Transduction and transmission of pain

Surgery-associated tissue injury activates the complex system which causes a patient to experience pain. Nociceptors are primary afferent fibres with normally only little spontaneous activity (Sorkin and Wallace 1999). These sensory fibres are named A-beta, A-delta and C-fibres according to their receptive modality and response to stimuli (Table 1) (Kalso and Kontinen 2009b). After an incision various proinflammatory agents, such as adenosine-5´-triphospate (ATP), nerve growth factor (NGF), tumour necrosis factor-alpha (TNF-α), bradykinin, prostaglandin E_2, serotonin and protons (H+) are released from the injured tissues and activate primary afferents (transduction) (Dawes et al. 2013). Nociceptors themselves are able to release substance P that further increases local inflammation. C-fibres have a higher activation threshold in the nonsensitized state than do A-delta and A-beta fibres (Voscopoulos and Lema, 2010; Ringkamp et al. 2013).

Table 1. Sensory fibres

Properties	Aβ	Aδ	C
Diameter	5-15 μm	1-5 μm	< 1 μm
Myelin	yes	yes	no
Conducting velocity	50 m/s	6-30 m/s	0.4-2.5 m/s
Modality	proprioception touch	mechano, thermal nociceptor	mechano, thermal, chemical nociceptor

Transmission of nociceptive signals involves multiple voltage- or ligand-gated channels, such as sodium, calcium and potassium channels (Porreca 2012). The transient receptor potential V1 (TRPV1) ion channel is the pain transducer that belongs to the TRP family of ion channels and is present on most heat sensitive receptors. After an incision, the increased release of proinflammatory agents enhances the activation of the TRPV1 receptor and the sensitivity to noxious stimuli (Caterina and Julius 2001; Voscopoulos and Lema 2010). TRPA1 is the other channel of the TRP family that has been found to act as a transducer of pain states (Kremeyer et al. 2010; Sousa-Valente J et al. 2014).

The pain sensation can be divided into "first pain" and "second pain". The first pain is the initial, short-term and sharp pain conducted by myelinated A-delta fibres. The later, diffuse, dull pain called "second pain" is conducted by unmyelinated C-fibres (Porreca, 2012).

The excitatory input from primary sensory afferents onto neurons in the dorsal horn is mediated by glutamate released from presynaptic terminals. The fast excitatory synaptic transmission, via alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and kainate subtypes of a glutamate receptor, is evoked by the low-frequency action potential discharge of the primary afferents. The repeated and intense noxious peripheral stimulation evokes a higher frequency discharge. This results in the release of neuropeptides and glutamate from the central nociceptor terminals and in the activation of N-methyl-D-aspartate (NMDA) receptors. (Salter 2012)

The dorsal horn is divided into separate laminae that receive inputs from different types of fibres and have different functions. Laminae I-II receive inputs from A-delta and C-fibres. Laminae III-V receive inputs from A-beta fibres and laminae V also inputs from A-delta fibres. Most neurons of laminae II are interneurons. The axons of interneurons terminate locally or in the other spinal segments. Laminae I and V are the source of most projection neurons to supraspinal sites. These neurons project to the thalamus, the parabrachial area and amygdale. Nociceptive inputs are further transmitted to the higher cortical centres (Porreca 2012).

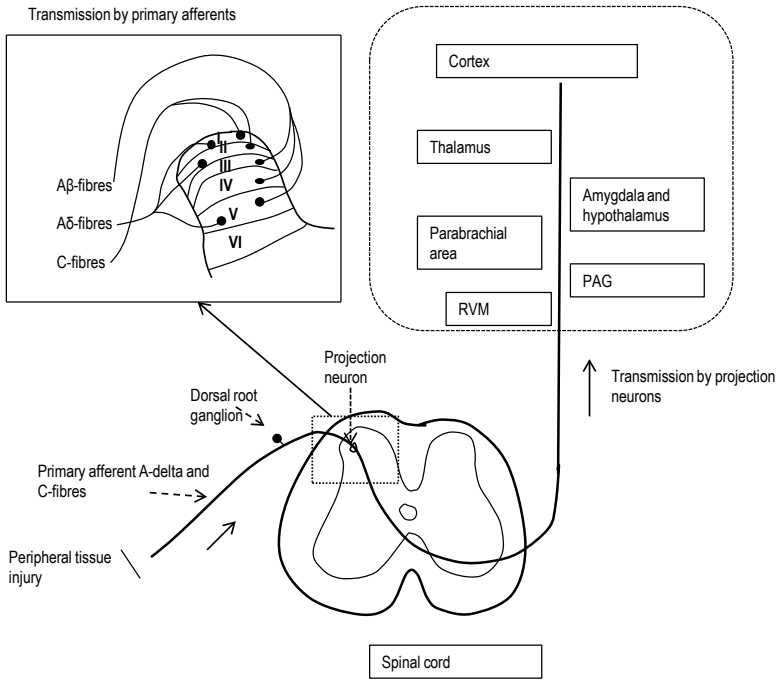

Figure 1. Transmission of pain. PAG = Periaquaductal grey. RVM = Rostral ventromedial medulla

2.1.2 Modulation of pain

The first specific pain system was presented in the 17th century. It was considered that painful input was transmitted from nociceptors to the brain passively along sensory channels (Bingel and Tracey 2008; Kalso and Kontinen 2009a). In 1965, Melzack and Wall published the gate control theory, which was the first significant theory to explain the pain modulatory system in the spinal cord. This theory was based on the interactions between thin diameter afferents (pain), large diameter afferents (touch, pressure, vibration), inhibitory interneurons and projection neurons. According to the theory the activity of large diameter afferents increases the inhibitory effect of interneurons and the activity of thin diameter afferents decreases it. This explains how non-painful stimuli can suppress pain perception (Melzack andWall, 1965; Kalso and Kontinen 2009a).

It is currently known that the descending pain modulatory network is the major system for the endogenous modulation of pain and that this modulation may be inhibitory or facilitatory (Bingel and Tracey 2008; Porreca 2012). This modulatory system originates in many regions of the central nervous system, the somatosensory cortex, hypothalamus, periaqueductal grey, pons, lateral tegmental area and rostroventral medulla. These structures interact with laminae I and V via the dorsolateral funiculus (Pubols et al. 1991). Neuroimaging studies have shown that higher level brain regions are involved in descending pain modulation. This may explain why emotions and cognitive factors have a role in pain modulation (Hadjipavlou et al. 2006; Bingel and Tracey 2008).

Two main neurotransmitters with an important role in descending modulation are norepinephrine and serotonin. Release of norepinephrine in the dorsal horn is connected with descending inhibition through activation of the α_2-adrenergic receptors (Millan 2002; D'Mello and Dickenson 2008). The effect of serotonin may be inhibitory or facilitatory depending on the subtype of the receptor (Millan 2002; Suzuki et al. 2004; Voscopoulos and Lema 2010). Endogenous opioids are also important transmitters in pain modulation at the level of spinal cord (Heinricher and Fields 2013). Furthermore, endocannabinois, acetylcholine, cholecystokinin, neurotensin and substance P contribute to pain modulation (Millan 2002).

The important inhibitory mechanism in the spinal dorsal horn is mediated by gamma-aminobutyric acid (GABA) and glycine receptors. GABA and glycine are

released from dorsal horn inhibitory interneurons involving the modulation of nociception (Salter 2012).

2.1.3 Perception of pain

Pain perception is a subjective experience that is not directly related to the nociceptive input. This pain experience is determined by an individual's biological, psychological and social characteristics (Figure 2).

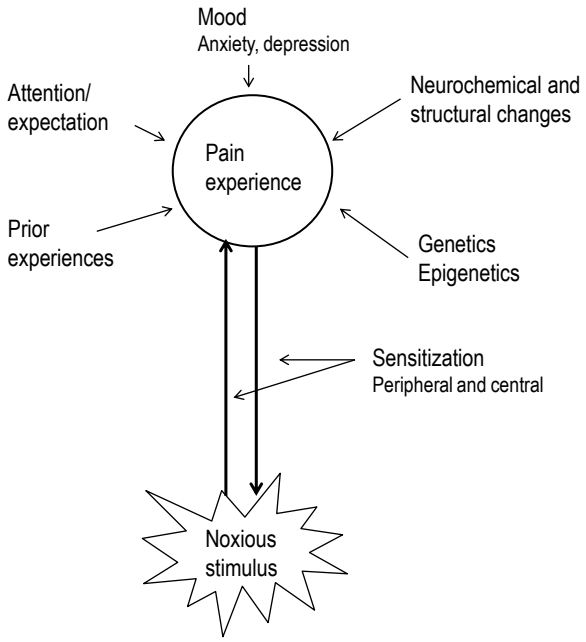

Figure 2. Pain perception (Modified from Bingel U and Tracey I: Imaging CNS modulation of pain in humans. Physiology 2008;23:371-380)

2.1.4 Sensitization

Tissue injury causes hypersensitivity in the area of a wound, called primary hyperalgesia, and in the adjacent tissue, called secondary hyperalgesia. Primary hyperalgesia is thought to be caused by the sensitization of primary afferent fibres, A-delta and C-fibre nociceptors. Primary hyperalgesia means a lowered threshold to both thermal and mechanical painful stimuli (Pogatzki-Zahn et al. 2007). This phenomenon is mediated by the tissue induced release of mediators, ischaemia and local acidosis (Woo et al. 2004). Secondary hyperalgesia is observed only to mechanical stimuli and is considered to be caused by the central sensitization of dorsal horn neurons (Zahn and Brennan 1999; Pogatzki-Zahn et al. 2007; Brennan 2011).

Wind-up and long-term potentiation are parts of central sensitization. Wind-up is known as the phenomenon in which the repetitive stimulation of C-fibres with constant stimuli activates NMDA receptors. At normal resting potential Mg^{2+} blocks the NMDA receptor. Under continuous stimulation the magnesium block is removed from the NMDA receptor channel and the response of second-order neurons to nociceptive stimuli is enhanced (Mendell and Wall 1965; Eide 2000).

Long term potentiation is the phenomenon whereby a brief high frequency stimulation of primary afferent fibres causes a persistent response (Randic et al. 1993).

The glial cells, microglia and astrocytes, have an important role in the molecular mechanisms involved in hypersensitivity in the dorsal horn. Microglia refers to non-neuronal cells of the brain and spinal cord, functionally equivalent to peripheral macrophages, which actively communicate with neurons (Steyaert and Kock 2012; Voscopoulos and Lema 2010). Tissue injury causes the stimulation of microglia, which contributes to central sensitization (Chacur et al. 2009). Animal studies have shown that the microglial inhibitor minocycline attenuates mechanical allodynia and central sensitization (Ledeboer et al. 2005; Chang and Waxman 2010). Whether the activation of microglial cells has a role in clinical pain is still uncertain (Salter 2012).

2.1.5 Mechanism of persistent postsurgical pain

Persistent postsurgical pain (PPSP) is defined as pain that develops after surgical intervention and lasts at least two months while other causes of pain are excluded

(Macrae 2001). Persistent pain is a complex phenomenon caused by various factors. Iatrogenic neuropathic pain as a result of surgery is thought to be the most common type of PPSP. A continuous inflammatory response has also been reported to have a critical role for persistent pain (Kehlet et al. 2006).

The increased inflammatory pain caused by tissue injury is a consequence of peripheral and central sensitization. The damage to the peripheral nerve causes both neuronal and immune changes that result in neuropathic pain. After nerve injury $Na_v1.8$ voltage-gated sodium channel is redistributed and microglial cells are activated in the spinal dorsal horn. These events cause long-term changes, such as gene expression in the dorsal root ganglia and the spinal cord, central sensitization, and transsynaptic neurogeneration. It has been assumed that ongoing inflammation or inflammatory mediators may maintain persistent neuropathic pain (Sheen and Chung 1993; Ito et al. 2009; Voscopoulos and Lema 2010; Calvo et al. 2012). Furthermore, it has been shown that postsurgical inflammatory neuropathies may develop without trauma to the nerves (Staff et al. 2010). Despite nerve injury, not all patients have neuropathic pain (Mikkelsen et al. 2004).

Genetic factors have been thought to explain the wide variations in pain sensitivity and in the development of persistent pain. It is evident that the issue of the heredity of persistent pain is complex because genetics is involved in the whole pain physiology from nociception to pain perception (Mogil 2012). The difference in pain sensitivity between patients may have an impact on developing persistent pain (Abrishami et al. 2011). Fibromyalgia, migraine, irritable bowel syndrome, irritable bladder, backache and Raynauds´s syndrome have been proposed to have genetic background which may predispose to persistent postsurgical pain (Voscopoulos and Lema 2010). A failure of descending modulation with pro- and anti-nociceptive components has been linked to chronic disorders that are associated with pain with no tissue pathology (Bingel and Tracey 2008).

In recent years epigenetic mechanisms have been linked to the development or maintenance of chronic pain states. Epigenetics is the study of processes that lead to stable and/or heritable changes in gene function without DNA sequence changes. Examples of epigenetic mechanisms include DNA methylation, histone modification and chromatin remodelling. Epigenetic processes are thought to be involved in the regulation of peripheral inflammation, the expression of nociceptive genes in chronic pain states, and plasticity and cortical pain processing. (Denk and McMahon 2012).

Psychosocial factors have an impact on pain progression from acute to persistent. An association between psychological vulnerability, stress and late return to work with persistent pain has been shown in many clinical studies of persistent postsurgical pain (Hinrichs-Rocker et al. 2009). A study of 18 patients, undergoing total knee arthroplasty and rating high scores on the Pain Catastrophizing Scale, reported that psychological intervention reduced pain severity compared with a cohort with usual postoperative care two months after surgery (Riddle et al. 2011).

The effects of drugs on central sensitization have been tested in experimental models in human volunteers. Ketamine is an NMDA receptor antagonist which has been shown to reduce central sensitization (Arendt-Nielsen et al. 1995). Gabapentinoids, gabapentin and pregabalin, act on the $\alpha^2\delta$ subunit of calcium channels. Gabapentinoids have been shown to reduce secondary hyperalgesia and central sensitization (Tuchman et al. 2010). Serotonin and norepinephrine are transmitters of descending modulation. In an animal study serotonin-norepinephrine reuptake inhibitor duloxetin reduced central sensitization (Iyengar et al. 2004). Opioids have analgesic effect that comes through the activation of μ-opioid receptor. Paradoxically, prolonged use of opioids and high intraoperative doses of remifentanil, an ultra-short acting opioid, may induce hyperalgesia (Fletcher and Martinez 2014). The mechanisms underlying opioid induced hyperalgesia seem to be multifactorial including peripheral, spinal and supraspinal mechanisms (Lee et al. 2011). The clinical impact of these drugs on the prevention of persistent postsurgical pain is not clear, and more clinical trials on the issue are needed (McGreevy et al. 2011).

2.2 Pain assessment

2.2.1 Pain measurement

Pain is a subjective experience with sensory, affective and evaluative qualities. Self-report is the most valid measure of pain. Acute pain is measured most frequently by only one of the pain rating scales intended to measure the intensity of pain. Often it is also essential to measure other dimensions of pain. Many pain questionnaires have been developed for that purpose (Melzack and Katz 2013).

The oldest of these is the McGill Pain Questionnaire (MPQ), which is still widely used in clinical and research settings (Melzack 1975).

2.2.1.1 Pain rating scales

Many self-report methods are used to measure the intensity of pain. The most commonly used one is a visual analogue scale (VAS). VAS is a ten centimetre long scale where a patient is asked to rate her or his pain with a horizontal line or triangle, the sharp corner meaning no pain and blunt end maximal pain. Numerical rating scale (NRS) refers to a scale from zero to ten when zero means "no pain" and ten "the worst possible pain". Pain can also be assessed on a verbal scale, e.g. no pain, mild, moderate and severe, or with a faces pain scale. These are all equally useful in clinical practice (Kalso and Kontinen 2009a) However, a verbal scale is not comparable with NRS and VAS in research settings (Kliger et al. 2015).

2.2.1.2 Pain questionnaires

The MPQ is a measure of pain which includes three major classes of verbal descriptors, an intensity scale and questions to determine the properties of the pain experience (Melzack 1975). It is the first valid verbal measure and, with its numerous modifications, is still used in pain studies. Because the MPQ has limitations in differentiating the qualities of pain, many other self-report measures have been developed for that purpose, for example the Neuropatic Pain Scale (Galer and Jensen 1997) and DN4 (Douleur Neuropathique 4 Questions) (Bouhassira et al. 2005).

2.2.2 Neuropathic pain assessment

Neuropathic pain has been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) (Treede et al. 2008).

Neuropathic pain is not a single disease but a syndrome with specific symptoms and signs. Because there is no specific diagnostic method for neuropathic pain, the

European Federation of Neurological Societies (EFNS) (Cruccu et al. 2010) and NeuPSIG (Haanpää et al. 2011) have proposed guidelines on neuropathic pain assessment. The EFNS guidelines are based on the grading system, possible, probable and definite neuropathic pain. The diagnosis is made by the history of pain, the clinical examination including touch/vibration, cold, warmth and pain sensibility and a diagnostic test, e.g. skin biopsy (Cruccu et al. 2010).

2.3 Predictors of postoperative pain

2.3.1 Predictors of acute pain

The first systematic review to identify factors predicting the severity of acute pain was published by Ip et al. This review included 48 studies published between 1983 and 2008 and found that young age, anxiety and type of surgery are predictive factors for the intensity of postoperative acute pain. The most painful surgical procedures were orthopaedics with major joint surgery, thoracic and open abdominal surgery (Ip et al. 2009).

A recent, large-scale prospective study of 1,490 patients undergoing heterogeneous surgical procedures found that preexisting pain and expected pain >40 measured by VAS (Visual Analogue Scale) score were the strongest predictors of moderate or intense postoperative pain. Other predictors of pain were pain catastrophizing and long-term fear. (M. Sommer et al. 2010) Preoperative pain was also a predictor for postoperative acute pain after elective ambulatory surgery (Gramke et al. 2009). Other predictors of pain in this cross-sectional study were postoperative pain anticipated by clinician or by patient, younger age or fear of the short-term consequences of the operation.

2.3.2 Predictors of persistent pain

Predictors of persistent postsurgical pain have been identified in many different studies concerning various surgical procedures (VanDenKerkhof et al. 2013). Table 2 presents a list of known predictors according to the perioperative phase. The

intensity of preoperative pain and acute postoperative pain have been shown to have an association with PPSP. Nerve injury is one of the most important predictive factors. Surgical procedures with a high risk of nerve damage, are associated with an increased risk of PPSP; e.g. thoracotomy, amputation and mastectomy (Niraj and Rowbotham 2011). Psychological factors, e.g. preoperative fear of surgery, depression and catastrophizing, have been shown to be associated with PPSP in many studies (Peters et al 2007; Niraj and Rowbotham 2011; VanDenKerkhof et al. 2012; Meretoja et al. 2014). Repeat surgeries, female gender, younger age in adults, genetics, social factors, radiation and neurotoxic chemotherapy have also been linked with PPSP (Kehlet et al. 2006; Macrae 2008; Voscopoulos and Lema 2010; Andersen and Kehlet 2011; Johansen et al. 2012; Bruce et al. 2014; Reddi and Curran 2014; Stephens et al. 2014; Belfer et al. 2015).

Table 2. Known predictors of persistent postsurgical pain

Preoperative factors	Recent references
Chronic pain	Meretoja et al. 2014
Preoperative pain at surgical site	VanDenKerkhof et al. 2012; Meretoja et al. 2014
Psychosocial factors	Peters et al. 2007; VanDenKerkhof et al. 2012
Young age in adulthood	Bruce et al. 2014
Heredity	Stephens et al. 2014; Belfer et al. 2015
Intraoperative factors	
Type of surgery with major risk of nerve damage and tissue ischaemia	Niraj and Rowbotham 2011; McGreevy et al. 2011; Haroutiunian et al. 2013
Postoperative factors	
Severe acute postoperative pain	VanDenKerkhof et al. 2012; Bruce et al. 2014
Radiation	Andersen and Kehlet 2011; Meretoja et al. 2014
Neurotoxic chemotherapy	Meretoja et al. 2014
Sensory changes in the surgical area	Johansen et al. 2012
Psychological factors	Johansen et al. 2012

2.4 Effect of anaesthetics on postoperative pain

General anaesthetics are a group of chemicals which suppress CNS activity and induce unconsciousness (Franks 2008). There are two kinds of general anaesthetics, intravenous and volatile.

The history of modern inhaled and intravenous anaesthetics is fairly short. The first inhaled anaesthetics, nitrous oxide, diethyl ether and chloroform were introduced between 1844 and 1847. Of the inhaled anaesthetics still in clinical use isoflurane was synthesized in 1965, desflurane in 1992 and sevoflurane in 1994. Intravenous anaesthesia became possible in the mid-nineteenth century with the development of the hollow needle for injection. The first barbiturate, barbital, was synthesized in 1903. Etomidate was synthesized in 1964 and propofol as late as in 1977 (Jacob et al. 2013).

The major mechanism of the action of intravenous anaesthetics thiopental, methohexital, propofol and etomidate is through GABA receptors (Reves et al. 2005). Volatile anaesthetics halothane, isoflurane, sevoflurane and desflurane can sensitize or activate GABA receptors but there are also other suggested mechanisms behind their effects on CNS activity (Rudolph and Antkowiak 2004). Opioids are used as analgesic agents during general anaesthesia. Common opioids in the intraoperative period are fentanyl, alfentanyl and ultra-short acting opioid remifentanil (Mandel 2014). Local anaesthetics can be combined with general anaesthetics or used alone. However, the role of local anaesthesia is not reviewed here.

2.4.1 Effect of anaesthetics on acute postoperative pain

Animal studies have shown that some general anaesthetics can stimulate peripheral nociceptors (Matta et al. 2008). Intravenous anaesthetics propofol and etomidate are known for their burning pain effect on injection (Tan and Onsiong, 1998). Some inhaled anaesthetics, e.g. isoflurane and desflurane, have a pungent odour and irritation of the airways limits their use in induction (TerRiet et al. 2000). It has been shown that pungent general anaesthetics activate and sensitize the Transient Receptor Potential (TRP) ion channel TRPA1, which is a principal receptor in the pain pathway. Non-pungent volatile anaesthetics, such as sevoflurane, have no effect on TRPA1 receptor (Matta et al. 2008). TRPV1 is a nociceptive ion channel

which is activated by irritant chemicals, e.g. capsaisin, and noxious heat. General anaesthetics also sensitize TRPV1 and this effect is milder with non-pungent volatile general anaesthetics than with pungent ones (Cornett et al. 2008).

In an animal model, inhaled anaesthetics halothane, isoflurane, nitrous oxide and diethyl ether produced hyperalgesia at low (0.1 MAC) concentrations, (Zhang et al. 2000) while isoflurane has been reported to cause analgesia at high concentrations (Flood et al. 2002). It is known that nitrous oxide is an inhaled anaesthetic with an acute analgesic effect at subanaesthetic concentrations (de Vasconcellos and Sneyd 2013). This is thought to be explained by the fact that the concentration needed to induce loss of consciousness is higher for nitrous oxide than for desflurane, isoflurane and sevoflurane (Zhang et al. 2000). The analgesic or antihyperalgesic effect of iv anaesthetic propofol has been studied in healthy volunteers. In the study by Bandsschapp et al. men experienced reduced pain and smaller areas of hyperalgesia and allodynia induced by intracutaneus electrical stimulation during target-controlled infusion (2ug/ml) of propofol. However, these analgesic effects of propofol disappeared shortly after cessation of the infusion (Bandschapp et al. 2010).

The clinical impact of anaesthetics on postoperative acute pain is uncertain. There are studies comparing inhaled anaesthetics with propofol in relation to the severity of postoperative pain, but with contradictory results (Boccara et al. 1998; Cheng et al. 2008; Fassoulaki et al. 2008; Tan et al. 2010; Li et al. 2012; Hasani et al. 2013; Ogurlu et al. 2014; Ortiz et al. 2014). Isoflurane compared with propofol has been shown to reduce pain scores (Boccara et al. 1998) or on the contrary to exacerbate pain (Cheng et al. 2008) in the acute postoperative phase. When propofol was compared with sevoflurane, four studies reported less pain after propofol anaesthesia (Tan et al. 2010; Li et al. 2012; Hasani et al. 2013; Ogurlu et al. 2014) and two studies found no difference in pain between groups on propofol and sevoflurane (Fassoulaki et al. 2008; Ortiz et al. 2014). Furthermore, no difference was found between propofol and desflurane (Fassoulaki et al. 2008; Ortiz et al. 2014) or propofol and isoflurane (Ortiz et al. 2014).

Opioid induced hyperalgesia (OIH) and opioid tolerance may have an impact on acute postoperative pain (Fletcher and Martinez 2014). There is some evidence that especially the intraoperative use of ultra-short-acting opioid remifentanil may enhance pain sensitivity and result in more intense pain after surgery. The development of OIH seems to be dose related (Guignard et al. 2000; Hansen et al. 2005; Lee et al. 2011; Fletcher and Martinez 2014). Propofol may also have some

effects on OIH. In an experimental human pain model the infusion of subhypnotic doses of propofol delayed and weakened remifentanil induced antianalgesia (Singler et al. 2007). A study on pain after breast cancer surgery showed that remifentanil hyperalgesia was seen after a high dose of remifentanil combined with sevoflurane but not with propofol. Hyperalgesia was not seen after a low dose of remifentanil (Shin et al. 2010).

2.4.2 Effect of anaesthetics on persistent postsurgical pain

Persistent pain after surgery is a complex phenomenon including physiological, psychological and social components. Only few studies have been presented on the potential role of anaesthetics in the risk of persistent pain. The ENIGMA trial with 640 patients comparing intraoperative nitrous oxide with nitrous oxide free anaesthesia found that nitrous oxide administration was associated with a reduced risk of persistent pain after non-cardiac major surgery (Chan et al. 2011). The prospective, randomized study by Song et al. comparing the prevalence of persistent post-surgical pain three and six months after thoracotomy in 366 patients receiving TIVA with propofol and reminfentanil or inhalation anaesthesia with sevoflurane found that the prevalence of persistent pain was lower after TIVA (Song et al. 2012). In a retrospective study by Cho et al. of 175 women who had undergone breast cancer surgery 2.5 to 4 years earlier, persistent pain among patients anesthetized with sevoflurane was compared with that among those receiving propofol anaesthesia. It appeared that sevoflurane anaesthesia was associated with a higher incidence of persistent pain. In this study all patients received intraoperative remifentanil combined with anaesthetics (Cho et al. 2013). In a prospective study of 120 cardiac surgery patients it was found that intraoperative remifentanil is a risk factor for persistent postsurgical pain (van Gulik et al. 2012). The role of remifentanil in persistent pain remained unclear in studies by Song et al. and Cho et al.(Song et al. 2012; Cho et al. 2013).

2.5 Effect of surgery on postoperative pain

Surgical techniques have changed dramatically since laparoscopic technique became a part of surgery. The first laparoscopic cholecystectomy was performed in France in 1987 by Mouret (Spaner and Warnock 1997). Although laparoscopy had

already become common in gynaecology in the 1970s, laparoscopic hysterectomy was first described as late as in 1989 (Reich et al. 1989; Riskin et al. 2006). Since the 1980s mini-invasive techniques have become increasingly popular in surgical procedures. The latest innovation in this field is robotic technology. Changes from open surgery to endoscopic and laparoscopic surgery have made a difference to postoperative pain.

The type of surgery is known to be one of the most significant predictors for both acute and persistent postoperative pain (Ip et al. 2009; Niraj and Rowbotham 2011). The most painful procedures are orthopaedics with major joint surgery, thoracic surgery and open abdominal surgery (Ip et al. 2009). In a large scale prospective study, Sommer et al. reported that the risk of moderate or severe acute pain is higher after surgery on the lower and upper extremities than after other types of surgical procedures (Sommer et al. 2010). Major orthopaedic surgery was also associated with severe pain in the cohort study of 50,523 patients in 105 German hospitals. This study evaluated the intensity of pain on the first postoperative day. The patients were asked to rate their worst pain since surgery (numerical rating scale 0-10). Pain scores among 179 different surgical groups were compared. The laparoscopic approach was reportedly less painful than open surgery. Surprisingly, pain scores were often high after minor surgery, including appendectomy, cholecystectomy, haemorrhoidectomy and tonsillectomy, mostly due to apparently inadequate pain management. Instead, after major open abdominal and thoracic surgery pain was rated mild (NRS 0-4). This was explained by the extensive use of epidural analgesia in this group of patients (Gerbershagen et al. 2013).

Persistent postsurgical pain has in most cases been considered neuropathic, although other mechanisms have also been identified. Surgical procedures with a major risk of nerve injury, such as thoracic or breast surgery, result in higher prevalence of persistent neuropathic pain (Haroutiunian et al. 2013). Even though the trunks of the major nerves may not have been totally transected, they may have been stretched or crushed and this can contribute to persistent pain (Katz and Seltzer 2009). On the other hand, it is known that nerve damage may be present without pain as has been shown after herniotomy (Aasvang and Kehlet 2010).

There is no specific data to show the effect of a single surgeon on the severity of postoperative pain. However, high operative volumes of a surgical unit are associated with lower incidence of chronic pain after breast cancer surgery, probably because of better surgical techniques (Tasmuth et al. 1999). Long

duration of surgery may have an influence on pain because of prolonged nociceptive stimulus during surgery which may lead to more severe acute pain, and this in turn may contribute to central sensitization and increased persistent pain (Peters et al. 2007; Ip et al. 2009). A skilful surgeon is likely to be more adept at avoiding nerve damage and other intraoperative complications, which, in turn, may also have an impact on pain.

2.6 Characteristics of persistent postsurgical pain

The aetiology of persistent postsurgical pain is complex and is not fully understood (Haroutiunian et al. 2013). It has previously been considered mainly neuropathic in nature and attributed to mechanical nerve damage. Other mechanisms involved in pain becoming chronic, such as inflammation, have subsequently been recognized (Kairaluoma et al. 2006; H. Kehlet et al. 2006; Guastella et al. 2011; Haroutiunian et al. 2013). A study of 23 patients showed that post-surgical neuropathies may be inflammatory without mechanical trauma, confirmed with nerve biopsy (Staff et al. 2010). Again, peripheral inflammation may lead to inflammatory reactions within the central nervous system and hence contribute to persistent pain (Deumens et al. 2013).

Studies of the characteristics of PPSP have mainly focused on the definition of the neuropathic component of pain. In the absence of neuropathic pain the cause of pain has been considered to be nociceptive. A systematic review of 281 studies on persistent postsurgical pain after 11 different types of surgical procedures determined the prevalence of neuropathic pain with the neuropathic pain probability grading system (Haroutiunian et al. 2013). The prevalence of neuropathic pain among patients with persistent postsurgical pain differed across surgical procedures. The prevalence was 66% after thoracic surgery, 68% after breast cancer surgery and 6% after total hip or knee arthroplasty (Haroutiunian et al. 2013). In a prospective French multicentre study of 2,397 patients undergoing different types of surgical procedures, about half of the cases of persistent pain were identified as neuropathic (Dualé et al. 2014). However, consistent with the results of Haroutiunian et al., there was wide variation in the type of surgery and the prevalence of neuropathic persistent postsurgical pain. The cumulative risk of neuropathic pain was 3.2% after laparoscopic inguinal hernia surgery and 37.1%

after breast cancer surgery estimated with the DN4 questionnaire (Dualé et al. 2014).

2.7 Pain after hysterectomy

Hysterectomy is one of the most common surgical procedures performed on women all over the world (Kovac 2014). In Finland 6,700 women undergo hysterectomy for benign conditions every year (Brummer et al. 2009), regardless of new alternative treatments (Hurskainen et al. 2004). Hysterectomy can be performed vaginally, laparoscopically or by laparotomy. Traditionally, abdominal hysterectomy has been the most common technique (Wilcox et al. 1994; Brummer et al. 2009). Nowadays less invasive vaginal and laparoscopic techniques have become more popular and abdominal hysterectomy is performed mostly due to large uterus (Brummer et al. 2009). Vaginal hysterectomy (VH) is regarded as the least invasive technique, even though the laparoscopic techniques have improved (Kovac 2014). There are many modifications of laparoscopic hysterectomies, named laparoscopic hysterectomy (LH), laparoscopically assisted vaginal hysterectomy (LAVH) and total laparoscopic hysterectomy (TLH). Robotic hysterectomy is the most recent laparoscopic technique. Despite different guidelines for determining the least harmful and most beneficial approach to hysterectomy, the choice of approach still depends on the surgeon's own experience or on local preferences (Candiani and Izzo 2010).

2.7.1 Acute pain after hysterectomy

The intensity of pain after surgery can be rated as mild, moderate or severe. The anticipated level of postoperative pain after hysterectomy is moderate (Sommer et al. 2008, Gerbershagen et al. 2013).

A Cochrane review of 34 trials in order to determine the most beneficial and least harmful method of hysterectomy concluded that vaginal hysterectomy should be performed in preference to abdominal hysterectomy when possible. If vaginal hysterectomy is not feasible, laparoscopic hysterectomy has some advantages over abdominal hysterectomy. The laparoscopic approach does not have any advantages over the vaginal route. It is noteworthy that pain was not included in the outcomes observed (Nieboer et al. 2009).

There are only few studies concerning the possible effect of hysterectomy technique on postoperative pain. Most of the studies comparing different approaches to hysterectomy have focused on perioperative complications, duration of surgery and the length of hospital stay. Mini-invasive technique is known to reduce postoperative pain (Saurland et al. 2010; Gerbershagen et al. 2013). This is also seen after hysterectomy when the abdominal approach is compared to laparoscopy (Garry et al. 2004; Schindlbeck et al. 2008). When laparoscopic hysterectomy is compared to vaginal hysterectomy the results are mixed. The only randomized trial with postoperative pain as a main outcome measure found that the severity of pain and the need for rescue analgesics were significantly higher after vaginal hysterectomy than after total laparoscopic hysterectomy (Ghezzi et al. 2010). There is another randomized study comparing vaginal technique with total laparoscopic technique with consistent results, but in this study pain was not the primary outcome (Candiani et al. 2009). The eVALuate study consisted four approaches to laparoscopic hysterectomy: laparoscopic hysterectomy, laparoscopically assisted vaginal hysterectomy, laparoscopic supracervical hysterectomy and total laparoscopic hysterectomy. When laparoscopic hysterectomies were compared with vaginal hysterectomy, no difference in pain scores was found, but in the laparoscopic group the need for opioids was smaller. However this study, too, used pain as a secondary outcome, and the pain management was not standardized (Garry et al. 2004). In contrast to other studies, in a study comparing vaginal hysterectomy with laparoscopically assisted vaginal hysterectomy, no difference in the use of analgesics during hospital stay after surgery was found. In this study, again, the consumption of analgesics was used as a secondary outcome (Soriano et al. 2001).

2.7.2 Persistent pain after hysterectomy

Chronic pelvic pain is a common gynaecological symptom. Its prevalence is similar to that of chronic back pain (Ahangari 2014). Pelvic pain is one of the symptoms leading to the decision to perform hysterectomy. On the other hand, hysterectomy may be a cause of chronic pelvic pain. This makes estimating the prevalence of persistent postsurgical pain after hysterectomy challenging.

The incidence of chronic pain after common surgical procedures is 5-57% and the intensity of pain is severe for 0-8% of patients (Haroutiunian et al. 2013;

Simanski et al. 2014; Fletcher et al. 2015). A review of 11 studies of hysterectomy for benign causes showed a 4.7-31.9% prevalence of chronic pain 1-2 years after hysterectomy. The total number of women participating was 4,651. No differences were found in the prevalence of pain between different approaches to hysterectomy. The heterogeneity of studies was considered to explain the wide variation in the results (Brandsborg et al. 2008). In a questionnaire and database study of 1,299 Danish women a 31.9% prevalence of chronic pain one year after hysterectomy was found (Brandsborg et al. 2007). The same researchers conducted a prospective study on 90 women who had undergone abdominal (57), vaginal (25) or laparoscopically assisted vaginal (8) hysterectomy (Brandsborg et al. 2009; Brandsborg et al. 2011). They found a 17% incidence of pelvic pain four months after surgery. However, most of this pain was reported to be "pain likely to be continuing from before surgery" (Brandsborg et al. 2009). These 90 women rated the intensity of pelvic pain 1 to 7 (median 3) during the past week assessed by NRS 1-10 (Brandsborg et al. 2011). In another prospective study of 186 women, who had undergone hysterectomy four months earlier, a 50% prevalence of persistent pain was reported (Pinto et al. 2012). Most of the women had experienced abdominal hysterectomy (135), while vaginal hysterectomy was performed on 34, and laparoscopically assisted vaginal hysterectomy on six women. In this study persistent postsurgical pain was defined as any kind of pain linked to the surgery (Pinto et al. 2012) whereas in the previous study persistent pain was considered relevant only if the pain affected daily living (Brandsborg et al. 2009; Brandsborg et al. 2011). In a study on 433 women who had undergone major elective gynaecological surgery (abdominal hysterectomy 303/433 and laparoscopic/vaginal hysterectomy 53/433) a 14% incidence of PPSP was reported (VanDenKerkhof et al. 2012). Montes et al. recently conducted a prospective multicentre pain incidence study of different kind of surgical procedures. They found 11.8% (49/416) and 25% (88/350) incidences of PPSP after vaginal and after abdominal hysterectomies respectively four months after surgery (Montes et al 2015).

Many predictive factors are associated with persistent postsurgical pain regardless of the type of surgery (Peters et al 2007; Montes et al. 2015). Some predictors are more specific, e.g. for breast cancer surgery (Meretoja et al. 2014). There are few studies on the risk factors for persistent pain after hysterectomy. In a questionnaire and database study of 1,299 women, the perioperative data on pain were collected retrospectively. In that study the factors associated with persistent pain one year after hysterectomy were preoperative pelvic pain, pain as an

indication for hysterectomy, previous caesarean section and any other pain except pelvic pain. Spinal block was associated with a reduced risk for persistent pain (Brandsborg et al. 2007). A prospective study on 90 women identified four risk factors for persistent pain four months after hysterectomy: preoperative pain other than pelvic pain, severe acute pain, poor quality of life and low control of pain. In contrast to the earlier study there was no association between the type of anaesthesia, such as spinal or general anaesthesia, and persistent pain (Brandsborg et al. 2009). These results support the findings of a previous randomized controlled trial of 89 patients who underwent vaginal hysterectomy. In that study the anaesthesia technique (spinal versus general anaesthesia) had no effect on pain 12 weeks after vaginal hysterectomy (Sprung et al. 2006). In the prospective study by VanDenKerkhof et al. the patients were analysed to find the preoperative predictors of persistent pain six months after surgery. Preoperative pain, early postoperative pain and preoperative anxiety were found to be independent predictors of persistent postsurgical pain (VanDenKerkhof et al. 2012). In the study by Pinto et al, preoperative anxiety was also associated with PPSP. In this study the other predictors were emotional illness representations, pain catastrophizing, age, pain due to other conditions, abdominal hysterectomy and Phannenstiel incision (Pinto et al. 2012).

There is some evidence that laparosopic technique decreases the likelihood of persistent pain compared with open surgery. This has been shown after hernia surgery (Grant et al. 2004; Kehlet 2008; Niccolai et al. 2015) and cholecystectomy (Stiff et al. 1994). This is thought to be a result of less nerve damage. The approach to hysterectomy had no effect on the prevalence of persistent pain after hysterectomy in the two previous studies by Brandsborg et al. In these studies, most women had undergone either abdominal or vaginal hysterectomy (Brandsborg et al. 2007; Brandsborg et al. 2009). Laparoscopic hysterectomy has become more popular only recently. The impact of laparoscopic surgical technique on persistent posthysterectomy pain is still uncertain.

According to a systematic review of predictors of chronic pelvic pain smoking is one of the risk factors (Latthe et al. 2006). Smoking also increases the risk for chronic back pain and other chronic pain states (Shi et al. 2010; Pisinger et al. 2011). However, the question whether smoking increases the risk for persistent pain after hysterectomy remains unresolved.

2.7.2.1 Characteristics of persistent pain after hysterectomy

Little is known about the characteristics of persistent pain after hysterectomy. In a study by Montes et al, the incidence of neuropathic pain after vaginal or abdominal hysterectomies, assessed using the DN4 questionnaire, was 24.5% and 44.3% respectively (Montes et al. 2015). In a study on 90 women by Brandsborg et al. 3.3% of the patients reported scar pain four months after hysterectomy, while no allodynia was found in the painful area on clinical examination (Brandsborg et al. 2009). The nature of PPSP after laparoscopic hysterectomy is not clear.

2.8 Health related quality of life

Hysterectomies for benign conditions are performed in expectation of alleviating the prehysterectomy symptoms. Health related quality of life (HRQoL) is a multidimensional issue, where both physical and psychosocial factors play a role. Most women are satisfied with the results of hysterectomy (Kjerulff et al. 2000). Hysterectomy for benign causes has been shown to improve HRQoL (Heliovaara-Peippo et al. 2013; Kuppermann et al. 2013). However, severe chronic pain in general is associated with HRQoL (Leadley et al. 2014) and even mild persistent postsurgical pain impacts on HRQoL (Kalliomäki et al. 2009; Kinney et al. 2012).

A 36-item short-form health survey (SF-36) is a widely used measure of generic HRQoL. This is a questionnaire assessing eight health concepts: general health, bodily pain, vitality, physical functioning, social functioning, role functioning/physical, role functioning/emotional and mental health (Ware and Sherbourne 1992). The SF-36 has been validated for Finnish population (Aalto et al. 1999).

3 AIMS OF THE STUDY

The aim of this thesis was to ascertain whether the choice of anaesthetic or surgical technique has an impact on postoperative pain, to study the prevalence of persistent pain and to clarify the characteristics of pain after hysterectomy. The specific aims were:

1. To find out whether the severity of acute postoperative pain after laparoscopic hysterectomy differs between patients anaesthetised with inhalational anaesthetic sevoflurane or with iv-anaesthetic propofol.
2. To study whether the choice of laparoscopic or vaginal approach has an impact on the acute phase postoperative pain after hysterectomy for benign causes.
3. To determine the prevalence of persistent pelvic pain after laparoscopic or vaginal hysterectomy six months after surgery.
4. To find out the intensity of persistent pelvic pain and possible predictors for pain.
5. To make a clinical analysis of persistent post-hysterectomy pain patients and to clarify the nature of such pain.
6. To study whether persistent pain has consequences to women´s health related quality of life.

4 MATERIAL AND METHODS

4.1 Patients

The study population consisted of 242 patients who underwent laparoscopic (n=150) or vaginal (n=92) hysterectomy with or without salpingo-oophorectomy for benign causes at Tampere University Hospital or Valkeakoski Regional Hospital between October 2008 and March 2013. Study I included 148 laparoscopic hysterectomy patients, Study II 74 laparoscopic and 90 vaginal hysterectomy patients. Study III included 139 laparoscopic and 88 vaginal hysterectomy patients. Study IV included 13 laparoscopic and 3 vaginal hysterectomy patients who had reported persistent pelvic pain six months after surgery. The letter inviting subjects to participate in Study IV had been sent to 56 patients reporting persistent pain in Study III.

The inclusion criteria were as follows: age < 70 years; American Society of Anesthesiologists (ASA) status classification I/II/III; body mass index <35kg/m². The exclusion criteria were as follows: diabetes; liver disease; present use of opioids; prolapsed uterus, allergies to any of the study medications.

4.2 Anaesthesia

4.2.1 Anaesthesia protocol

All patients were premedicated with oral midazolam 7.5 mg and cetirizine 10 mg. Anaesthesia was induced with intravenous (IV) propofol 2-3 mg/kg (Study I) or using a target controlled infusion (TCI) of propofol (Schnider et al. 1998) (Studies I and II). Anaesthesia was maintained with sevoflurane (Study I) or a target controlled infusion of propofol (Studies I and II). A target controlled infusion of remifentanil (Minto et al. 1997) was initiated at the induction of anaesthesia and

continued to the end of anaesthesia. After the induction of anaesthesia all patients were given IV dexamethasone 5 mg to prevent nausea and vomiting. Rocuronium 0.6 mg/kg was given intravenously to facilitate endotracheal intubation. The lungs of the patients were mechanically ventilated with a mixture of oxygen in air. The delivery of anaesthetic was adjusted to maintain blood pressure and heart rate +/- 20% of the preoperative value, and State Entropy (Entropy, GE Healthcare, Helsinki, Finland) index value below 60. At the end of the surgery remifentanil infusion was discontinued and IV fentanyl 0.5 mg and paracetamol 1 g were given. All patients received IV neostigmine 2.5 mg with glycopyrrolate 0.5 mg to reverse neuromuscular blockade.

4.2.2 Randomization

The patients in Study I were randomized into two groups using a computer generated random number table. Anaesthesia was maintained either with propofol or sevoflurane. The patients were blinded to the group allocation.

4.3 Surgery

The approach to hysterectomy, laparoscopic or vaginal, was determined by the surgeon before the patient's written informed consent was obtained.

4.3.1 Vaginal hysterectomy

A local anaesthetic, lidocaine with adrenaline, was injected under the cervical mucosa. After that a circumferential incision was made and the vaginal mucosa was dissected from the cervix. The peritoneal cavity was entered via posterior cul de sac. The parametrial tissue, uterine vessels, ovarian vessels and fallopian tubes or with patients undergoing salpingo-oophorectomy the infundibulopelvic ligaments were ligated with sutures and the uterus was removed. Finally the vaginal wall was closed with an absorbable continuous suture.

4.3.2 Laparoscopic hysterectomy

The laparoscopic method included laparoscopic hysterectomies (LH) and laparoscopically assisted vaginal hysterectomies (LAVH). The pneumoperitoneum was created by inserting a Veress needle into the abdominal cavity through the umbilicus. If intra-abdominal adhesions were suspected Hasson's technique was used for entry. A 10 mm trocar was used for the camera and an additional three trocars of 5 mm were inserted laterally of both epigastric arteries and in the midline above the symphysis. Bipolar forceps for electrocautery were used to create haemostasis. The uterine arteries were controlled laparoscopically with bipolar electrocoagulation or vaginally with sutures in LH and LAVH, respectively. A local anaesthetic, i.e. lidocain with adrenaline, was injected under the cervical mucosa before the vaginal incision and the uterus was removed through the vagina. Finally the cuff was closed with a vaginal continuous suture.

4.4 Management of postoperative pain and nausea

For postoperative analgesia, IV oxycodone was given using a patient controlled analgesia (PCA) infusion pump in the postanaesthesia care unit (PACU) and on the ward, for at least 20 hours after surgery. The pump was programmed to deliver a 2 mg dose of oxycodone on demand with a lock-out time of 10 min. The rescue medication in the PACU was IV bolus of oxycodone 3 mg, given by the nurse if the patient assessed her pain >3 on the NRS. IV paracetamol 1 g was given every six hours. The rescue medication for nausea was either IV ondansetron 4 mg or IV droperidol 0.75 mg.

4.5 Clinical examination

Clinical examination was performed on all patients involved in Study IV. The examinations were performed in a lithotomy position. Sensory examination consisted sensory testing with a cotton stick, warm (+40C), cold (+25C) and toothpicks (Table 3). The area for sensory testing was above the umbilicus until the perineum and upper thighs and laterally from one iliac crest to the other. The gynaecological examination consisted of inspection and palpation of the vulva, vagina and pelvic area. All patients moreover underwent transvaginal ultrasound.

Table 3. Clinical testing to assess all sensory modalities

Fibre	Sensation	Testing
Aβ	Touch	Cotton stick
	Vibration	Tuning fork (128Hz)
Aδ	Pinprick	Toothpick
	Cold	Thermoroller
C	Warm	Thermoroller

4.6 Data collection

4.6.1 Studies I and II

Patients´ general characteristics and characteristics of the surgery were collected from the medical records. From the period in the PACU and on the ward until 20 hours after surgery the following data were collected: cumulative amount of oxycodone, NRS pain scores (scale 0-10) at rest and when coughing, NRS scores (scale 0-10) for nausea, number of episodes of postoperative vomiting, and sedation scores measured on a 4-point scale (0=fully awake; 1= awake but still sedated; 2= asleep but responds to verbal command; 3= unresponsive). The time of arrival at the PACU was recorded as time point 0 and all data were collected at time points 10 min, 20 min, 30 min, 60 min, 2 h, 4 h, 6 h and 20 h.

4.6.2 Study III

The data regarding the patients´ characteristics and surgical outcomes were collected from the patients´ medical records. The data regarding preoperative pain and the acute postoperative phase were collected from the data records of Studies I and II. A questionnaire with a prepaid response envelope was sent to all patients six months after hysterectomy. When necessary, a reminder was sent after one month. The questionnaire contained questions about the presence of persistent pain, intensity and character of the pain, sleep disorders and the effect of persistent pain on daily activities. The English translation of the questionnaire is shown in Appendix 1.

4.6.3 Study IV

All records of the perioperative phase and six months after hysterectomy were collected from the data of Studies I, II and III. After an appointment the patients completed the same pain questionnaire as in Study III and a generic health status measure SF-36, which is used to assess health related quality of life (Ware and Sherbourne 1992). Data on the clinical examinations were drawn and written on a chart designed for this purpose.

4.7 Statistics

The sample size estimation for Studies I and II was based on an earlier study of laparoscopic hysterectomies where the mean consumption of oxycodone during 24 hours was 0.45 (SD 0.24) mg/kg (Jokela et al. 2008) .Seventy-five patients per group were needed to show a 25% difference in the need for oxycodone with a power of 0.8 and α of 0.05. Because Study III was a follow-up study and Study IV a descriptive study, no power analyses for these studies were performed.

Results are shown as means and standard deviation (SD) or medians and interquartiles for numerical variables and as numbers and percentages for categorical variables. Independent sample t-test was used to analyse normally distributed continuous variables. Mann-Whitney was used to analyse skewly-distributed continues variables. Chi-Square or Fisher's exact test were used to assess differences in categorical variables. Repeated measures of ANOVA was used to compare the cumulative consumption of oxycodone and NRS scores for pain and nausea (Study I). Univariate logistic regression model was used to identify factors related to persistent post-hysterectomy pain. Variables with P value <0.20 in the univariate analysis were included in the final *(forward stepwise)* multivariable logistic regression analysis. (Study III). Differences between groups were considered significant at P <0.05. The statistical analysis was performed using SPSS™, Windows version 20.0 (SPSS Inc.; Chicago, IL., USA

4.8 Ethical considerations

Written informed consent was obtained from all patients and the studies were approved by the local ethics committee. Due to its classification as pharmaceutical research, Study I was also approved by the National Agency for Medicines. All studies were registered with Clinical Trials.

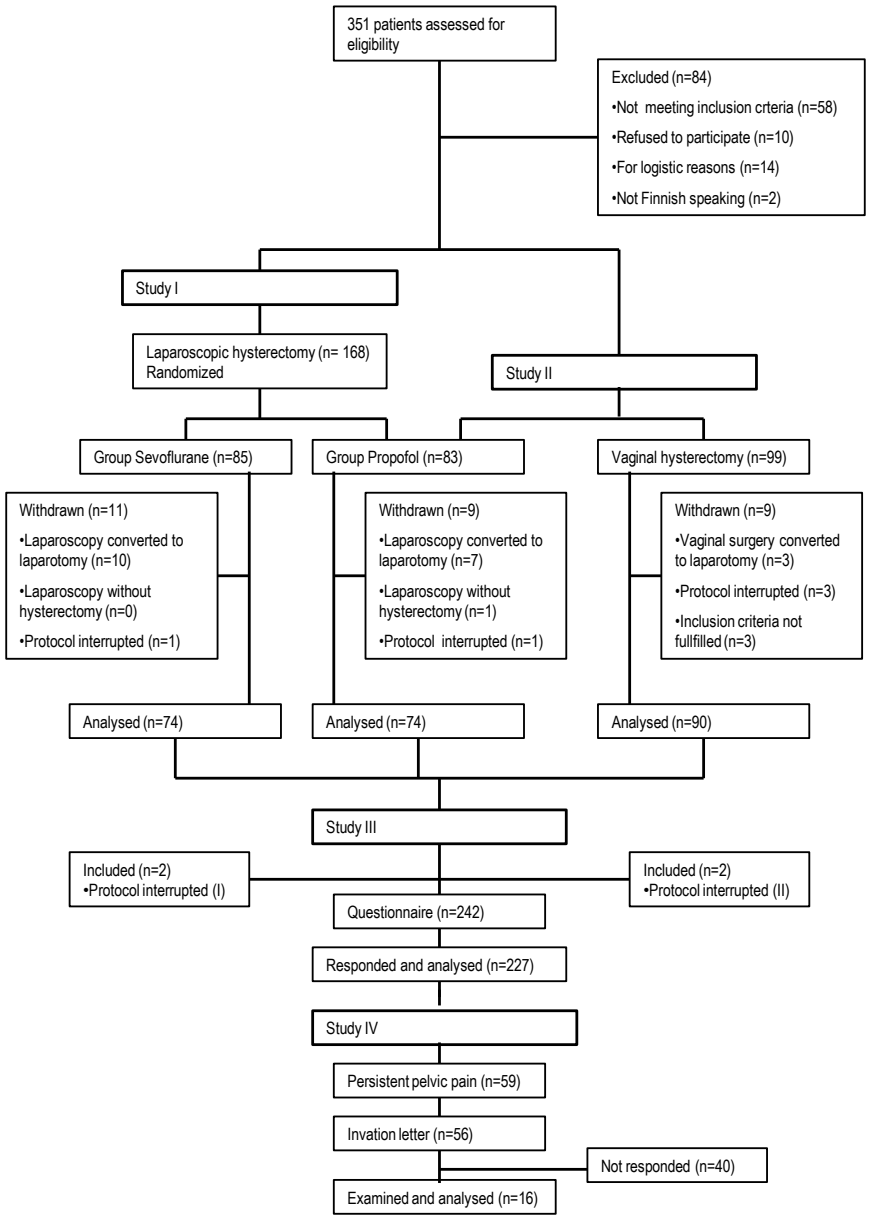

Figure 3. Flowchart of study patients

5 RESULTS

The flowchart of the patients is shown in Figure 3. Four patients were withdrawn from the analyses of Studies I and II because the PCA medication was discontinued or the records of data were otherwise missing before 20 hours had elapsed after the end of the operation. Study III consisted of 227 respondents. The characteristic of patients are presented in Table 4.

Table 4. Baseline characteristics of patients

	LH propo (Study I + II)	LH sevo (Study I)	VH (Study II)	(Study III)	(Study IV)
	n=74	n=74	n=90	n=227	n=16
Age (yr)	50.2 (7.2)	50.6 (7.9)	47.5 (6.3)	49 (7.2)	51 (6.6)
Weight (kg)	70.7 (12.2)	70.0 (10.9)	71.1 (10.4)		71.5 (12.3)
Height (cm)	165.8 (6.0)	165.2 (5.5)	165.3 (4.9)		163.7 (6.0)
Smoking	10 (13.5%)	11 (14.9%)	24 (26.7%)	41 (18.1%)	6 (37.5%)
Main indication for surgery					
Uterine leiomyoma	50 (67.6%)	39 (52.7%)	68 (76.6%)	148 (65.2%)	9 (56.3%)
Menstrual disorders	13 (17.6%)	18 (24.3%)	15 (16.7%)	45 (19.8%)	4 (25.0%)
Pelvic pain	3 (4.1%)	1 (1.4%)	6 (6.7%)	9 (4.0%)	0 (0.0%)
Other	8 (10.8%)	16 (21.6%)	1 (1.1%)	25 (11.0%)	3 (18.8%)

Values are mean (SD) or n (%). LH=laparoscopic hysterectomy, VH=vaginal hysterectomy, propo=propofol, sevo=sevoflurane

5.1 Postoperative acute pain and anaesthetics (Study I)

The choice of anaesthetic did not have an effect on postoperative acute pain. The consumption of oxycodone 20 hours after surgery did not differ between patients who had been anaesthetized with sevoflurane or propofol during laparoscopic hysterectomy. The NRS pain scores, either at rest or with coughing, were similar for patients receiving sevoflurane or propofol during the 20-hour period after hysterectomy. (Table 5)

The patients had significantly higher mean NRS scores for nausea during the first postoperative hour in the sevoflurane group (0.69-1.53) than in the propofol group (0.03-0.24) ($P<0.01$). The need for antiemetics also was greater in the sevoflurane group (median 0, Q_1- Q_3 0-1) than in the propofol group (median 0, Q_1- Q_3 0-0) ($P=0.018$).

5.2 Postoperative acute pain and surgical technique (Study II)

The consumption of oxycodone was smaller after laparoscopic hysterectomy than after vaginal hysterectomy at time point 4 hours ($P=0.040$) and at time point 6 hours ($P=0.026$) after surgery. The total consumption of opioid during the 20-hourperiod was similar in both groups. The postoperative pain scores at rest were significantly higher after vaginal hysterectomy at time point 60 min ($P=0.026$). (Table 6) The NRS pain scores with coughing did not differ between the groups.

The most common main indication for hysterectomy in both groups was uterine leiomyoma (Table 7). Uterus weight was similar in both groups (median 216, Q_1- Q_3 150-330 in the VH group and median 200, Q_1- Q_3 135-334 in the LH group) ($P=0.486$). For the patients undergoing laparoscopic hysterectomy duration of surgery (min) was longer (median 131, Q_1- Q_3 104-167) than for those undergoing vaginal hysterectomy (median 64, Q_1-Q_3 46-78) ($P<0.001$). The patients in the LH group stayed in hospital for a longer time, namely over one day for 41% of patients, compared to 10% of those in the VH group ($P= 0.001$).

Table 5. Cumulative consumption of oxycodone and NRS pain scores (0-10) at rest and with coughing 20 hours after surgery.

	Propofol (n=74)	Sevoflurane (n=74)	P value
Cumulative oxycodone dose (mg)			0.813
10 min after surgery	1.8 (2.3)	1.5 (1.7)	
20 min	4.3 (3.5)	3.9 (2.6)	
30 min	7.1 (4.3)	6.1 (3.2)	
60 min	10.5 (5.2)	9.8 (4.3)	
2 hours	14.8 (6.3)	13.9 (6.09	
4 hours	19.9 (7.7)	19.9 (9.6)	
6 hours	23.5 (8.9)	23.5 (12.4)	
20 hours	42.5 (17.7)	42.9 (23.8)	
NRS pain scores at rest (0-10)			0.328
10 min after surgery	4.5 (2.5)	3.7 (2.3)	
20 min	5.0 (2.4)	5.0 (2.2)	
30 min	5.0 (2.3)	4.9 (2.1)	
60 min	4.3 (2.2)	4.1 (2.1)	
2 hours	3.1 (2.0)	3.1 (2.1)	
4 hours	2.6 (2.0)	2.3 (1.6)	
6 hours	2.4 (2.1)	1.9 (1.8)	
20 hours	1.5 (1.6)	2.0 (2.0)	
NRS pain scores with coughing (0-10)			0.783
10 min	4.8 (2.6)	4.0 (2.4)	
20 min	5.3 (2.5)	5.6 (2.3)	
30 min	5.4 (2.3)	5.5 (2.1)	
60 min	4.9 (2.4)	4.9 (2.1)	
2 hours	4.0 (2.1)	4.0 (2.1)	
4 hours	3.7 (2.2)	3.5 (1.8)	
6 hours	3.6 (2.3)	3.3 (1.9)	
20 hours	2.8 (2.0)	3.2 (2.0)	

Values are mean (SD). NRS=numeric rating scale

Table 6. Cumulative consumption of oxycodone and NRS pain scores (0-10) at rest 20 hours after surgery

	LH (n=74)	VH (n=90)	P value
Cumulative oxycodone dose (mg)			
10 min after surgery	1.8 (2.3)	1.9 (2.0)	0.844
20 min	4.3 (3.5)	4.5 (2.7)	0.709
30 min	7.1 (4.3)	6.6 (3.4)	0.417
60 min	10.5 (5.2)	11.0 (4.7)	0.491
2 hours	14.8 (6.3)	16.6 (7.3)	0.090
4 hours	19.9 (7.7)	22.8 (10.3)	0.040
6 hours	23.5 (8.9)	27.4 (12.6)	0.026
20 hours	42.5 (17.7)	45.4 (21.2)	0.349
NRS pain scores at rest (0-10)			
10 min after surgery	4.5 (3-6)	5 (4-7)	0.101
20 min	5 (3-7)	5 (4-7)	0.224
30 min	5 (4-7)	5(4-7)	0.727
60 min	4 (3-6)	5 (4-7)	0.026
2 hours	3 (2-4)	3 (2-5)	0.305
4 hours	2.5 (1-4)	3 (1-4)	0.960
6 hours	2 (1-3.75)	2 (1-4)	0.637
20 hours	1 (0-2)	2 (1-3)	0.114

Values are mean (SD) or median (Lower quartile -Upper quartile)
LH= laparoscopic hysterectomy, VH=vaginal hysterectomy, NRS=numeric rating scale

Table 7. Characteristics of surgery (Reproduced with permission of Springer-Verlag)

	VH (*n* =90)		LH (*n*=74)		
	n	%	n	%	P value
Main indication of surgery					
Uterine leiomyoma	68	75.6	50	67.6	0.257
Menstrual disorders	15	16.7	13	17.6	0.879
Pelvic pain	6	6.7	3	4.1	0.465
Other	1	1.1	8	10.8	0.007
Type of surgery					
Hysterectomy with SO	6	6.7	42	56.8	<0.001

VH = vaginal hysterectomy, LH = laparoscopic hysterectomy, SO = salpingo-oophorectomy

5.3 Persistent pelvic pain after hysterectomy (Studies III and IV)

5.3.1 Prevalence of persistent pelvic pain

In Study III, the response rate was 94% (227 respondents out of 242), and the participation rate was 29% (16 out of 56 women) in Study IV.

The prevalence of persistent pelvic pain six months after surgery was 26.0% among all patients and 18.9% among the patients who had no pain before hysterectomy. Of all patients, 31.6% suffered from preoperative pelvic pain. Ten out of sixteen patients in Study IV still had persistent pelvic pain at the time of the clinical examination. In this study, the median time from hysterectomy to examination was 30 months (range 10-44).

5.3.2 Factors associated with persistent pelvic pain

Multivariable logistic regression revealed a significant association between persistent pain six months after hysterectomy and smoking, severe acute pain after surgery or laparoscopic surgical technique (Table 8). There was also a significant association between the intensity of preoperative pain and persistent pain in the univariate analysis; however the association was no longer significant in the multivariable model.

5.3.3 Characteristics of persistent pelvic pain

Only two of the 58 (3.4 %) patients who suffered persistent pelvic pain rated their average pain as severe (NRS 7-10), and 38 of the 58 (65.5%) patients as mild (NRS 0-3), six months after surgery (Study III). During the past week, the pain at its worst was classified as severe by four of the 58 (6.9 %) patients. Most of the patients did not have daily pain and the nature and location of the pain was variable. (Figure 4).

During the past week before the clinical examination (10-44 months after hysterectomy) five out of ten patients rated the average pain as moderate (NRS 4-6), one as mild (NRS 0-3) and one as severe (NRS 7-10) according to the questionnaire (Study IV). One patient had had no pain during the past week. Two patients had not completed the pain questionnaire regarding the intensity of pain. Most of the patients had pelvic pain less than once a week and only one patient had incessant and constant pain. The nature of the pain was mostly described as tenderness, but sometimes also as ache or as a burning sensation. According to the questionnaire and clinical examination pain was regarded as PPSP in nine patients and as probable neuropathic PPSP in five, and possibly or unlikely to be neuropathic in three patients and one patient respectively. The most common sensory dysfunction reported was hyperesthesia in the sensory area of the iliohypogastric nerve.

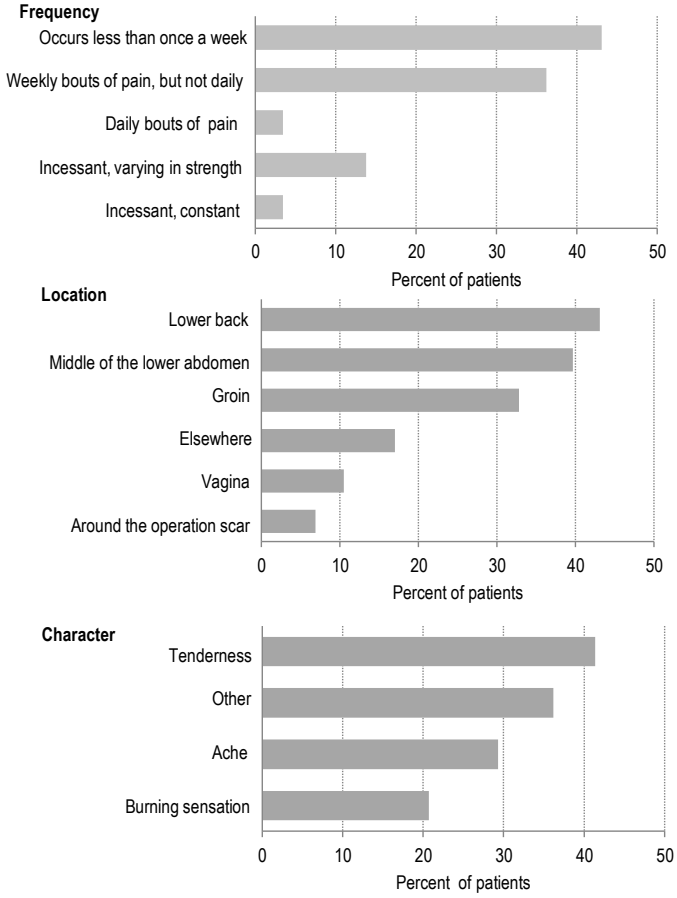

Figure 4. Characteristics of persistent pelvic pain six months after surgery

5.3.4 Health related quality of life

There were lower scores on all scales assessed by SF-36 compared with the Finnish general female cohort (Aalto et al. 1999). The Finnish female cohort consisted of 1,133 women aged 18 – 79 years. The significance was not determined because of the small number of study patients. (Study IV)

Table 8. Factors associated with persistent pain six months after hysterectomy (Reproduced with permission of Wolters Kluwer Health Lippincott Williams & Wilkins)

	Persistent pain		Univariate		Multivariable	
	n	percent	OR (95% CI)	P	OR (95% CI)	P
All patients (n=227)	59	26.0				
Pain at rest 1h after surgery (NRS 0-10)			1.10 (0.96-1.27)	0.167		
NRS 0-3 (n=69)	15	21.7				
NRS 4-6 (n=111)	29	26.1				
NRS 7-10 (n=47)	15	31.9				
Pain with coughing 1h after surgery (NRS 0-10)			1.13 (0.99-1.30)	0.080		
NRS 0-3 (n=50)	7	14.0				
NRS 4-6 (n=108)	32	29.6				
NRS 7-10 (n=67)	19	28.4				
Pain at rest 4h after surgery (NRS 0-10)			1.26 (1.07-1.49)	0.007		
NRS 0-3 (n=160)	34	21.3				
NRS 4-6 (n=57)	21	36.8				
NRS 7-10 (n=6)	3	50.0				
Pain with coughing 4h after surgery (NRS 0-10)			1.26 (1.08-1.47)	0.003	1.22 (1.02-1.44)	0.025
NRS 0-3 (n=122)	25	20.5				
NRS 4-6 (n=81)	23	28.4				
NRS 7-10 (n=18)	9	50.0				
Preoperative pain at rest (NRS 0-10)			1.28 (1.09-1.51)	0.004		
NRS 0-3 (n=188)	45	23.9				
NRS 4-6 (n=17)	7	41.2				

NRS 7-10 (n=4)	2	50.0				
Preoperative pain during motion (NRS 0-10)			1.20 (1.05-1.38)	0.010		
NRS 0-3 (n=180)	42	23.3				
NRS 4-6(n=21)	9	42.9				
NRS 7-10 (n=8)	3	37.5				
Smoking						
Yes (n=41)	19	46.3	3.23 (1.59-6.57)	0.001	3.80 (1.67-8.67)	0.001
No (n=185)	39	21.1	Reference			
Type of surgery						
Laparoscopic (n=139)	43	30.9	2.02 (1.05-3.87)	0.035	2.43 (1.12-5.24)	0.024
Vaginal (n=88)	16	18.2	Reference			
Complication						
None (n=185)	45	24.3	Reference			
All together (n=42)	14	33.3	1.56 (0.75-3.21)	0.232		
Haematoma (n=19)	5	26.3				
Infection (n=16)	5	31.3				
Other (n=7)	4	57.1				
Anaesthetic						
Propofol (n=158)	41	25.9	1.00 (0.52-1.89)	0.983		
Sevoflurane (n=69)	18	26.1	Reference			
	Mean	SD				
Age (y)	48.9	7.3	0.99 (0.95-1.03)	0.504		
Remifentanil consumption (10ug)	119.1	48.8	1.01 (1.00-1.01)	0.125		

NRS=Numeric rating scale

6 DISCUSSION

The experience of pain is a complex, multifactorial issue. After the same surgical procedure the severity of pain and the need for analgesics differ significantly between patients due to many known factors, such as age, gender, mood, anxiety, drug-drug interactions and genetics (Yang et al. 2000; Ren et al. 2015). Nevertheless, a single factor may have an important role in the attempt to lessen postoperative pain.

6.1 Acute postoperative pain

6.1.1 Acute postoperative pain and the role of anaesthetics

In Study I the choice of anaesthetic between propofol and sevoflurane for the maintenance of anaesthesia during laparoscopic hysterectomy had no impact on the severity of pain and need for opioids during the first 20 postoperative hours. This concurs with the study by Fassoulaki et al. reporting no differences between propofol, sevoflurane or desflurane and postoperative morphine consumption and pain scores, (Fassoulaki et al. 2008) and also with the study by Ortiz et al, where propofol, isoflurane, desflurane and sevoflurane were compared (Ortiz et al. 2014). Yet there are also contradictory results showing the superiority of propofol over volatile anaesthetics (Cheng et al. 2008; Tan et al. 2010, Li et al. 2012; Hasani et al. 2013; Ogurlu et al. 2014) or the superiority of isoflurane over propofol (Boccara et al. 1998) with relation to postoperative pain.

The inadequate sample size, differences in the study protocols and the chosen primary outcomes may explain the discrepancy between the results of earlier studies. The study by Tan et al. concerned day-surgery patients (Tan et al. 2010) and the study by Hasani et al. concerned children aged three to six years, who were observed only for two hours postoperatively (Hasani et al. 2013). In the rest of the studies the patients were monitored for at least eight hours. In most of the earlier studies the primary outcome has been the severity of pain, whereas in Study I and

in the study by Fassoulaki et al. (Fassoulaki et al. 2008) the cumulative consumption of opioid was used as the primary outcome measurement.

Anaesthetics are not a uniform group of medicines. They can be divided into two subgroups, volatile and intravenous anaesthetics. However, this classification only defines how the anaesthetic is administered to the patient. Each anaesthetic has a unique profile of effects. It is known that some inhaled anaesthetics, e.g. isoflurane and desflurane, irritate the airways, which excludes their use as induction agents. The volatile anaesthetic sevoflurane does not have this irritative effect. Again, some intravenous anaesthetics, e.g. propofol, may cause burning pain during injection. If propofol had an advantage over volatile anaesthetics as regards acute postoperative pain, what would be the mechanism behind it? The evidence of differences in the properties of anaesthetics to activate and sensitize the TRPA1 and TRPV does not support the claim about the superiority of propofol (Cornett et al. 2008; Matta et al. 2008). Again, although it has been shown in healthy volunteers that propofol infusion reduced experimentally produced pain, this effect disappeared when the infusion was discontinued (Bandschapp et al. 2010).

6.1.2 Acute postoperative pain and the role of surgery

The pain scores at the time point one hour postoperative and the cumulative amount of oxycodone consumed at time points four and six postoperative hours were lower after laparoscopic hysterectomy than after vaginal hysterectomy in Study II. This was also the case in a randomized study by Ghezzi et al, where total laparoscopic hysterectomy was compared with vaginal hysterectomy and where pain was used as the main outcome measure, with similar results (Ghezzi et al. 2010).

Other studies in this field have described mixed results. However, in these studies pain has been only a secondary outcome (Soriano et al. 2001; Garry et al. 2004; Candiani et al. 2009; Sesti et al. 2014). Laparoscopic route was associated with less pain in the study comparing VH with LH (Garry et al. 2004) and in the study comparing VH with TLH (Candiani et al. 2009). The recent randomized study (Sesti et al. 2014) comparing TLH, LAVH and VH and the earlier study (Soriano et al. 2001) comparing LAVH and VH found no difference in the severity of postoperative pain.

Laparoscopic surgical technique has managed to reduce postoperative pain after different kinds of surgical procedures compared with open technique (Garry et al.

2004; Saurland et al. 2010; Gerbershagen et al. 2013). Vaginal hysterectomy has been named the least invasive technique of hysterectomy (Kovac 2014). Despite this, the results of Study II indicate that acute postoperative pain is more severe after vaginal hysterectomy than after laparoscopically assisted vaginal or laparoscopic hysterectomy. This finding concurs with that of Ghezzi et al. showing that acute pain was less after total laparoscopic hysterectomy than after vaginal hysterectomy (Ghezzi et al. 2010). What makes the vaginal approach more painful? One explanation could be that in the vaginal technique detaching of the uterus demands a forceful traction on the adjacent tissue which is not necessary when the uterus is detached laparoscopically. The other difference is in the management of bleeding. In Study II the vessels were ligated with sutures in the vaginal group whereas electrocautery was used to manage haemostasis in the laparoscopic group. This may have an impact on postoperative pain (Lakeman et al. 2012).

6.1.3 Acute pain assessment

Studying acute postoperative pain in order to ascertain the significance of one single factor in pain is challenging. The perception of pain is a subjective experience formed by numerous factors, thus it may be difficult to demonstrate the significance of specific factor. Pain scores or analgesic consumption are commonly used to assess the severity of postsurgical pain. Both methods, pain scores and analgesic consumption, have their weaknesses. A pain rating scale is not an objective pain measurement, all analgesics have side effects which may affect consumption and the severity of pain differs enormously between patients after the same surgical procedure. All this contributes to pain assessment.

6.2 Persistent postsurgical pain

6.2.1 Prevalence and intensity of persistent pain after hysterectomy

The results of Study III showed that persistent pelvic pain is common after laparoscopic or vaginal hysterectomy, but the intensity of pain usually remains mild and in most patients the pain is not incessant. Among all patients in these studies the prevalence of persistent pelvic pain was 26.0% (59/227). In these patients, the

prevalence of new pain, i.e. pain not experienced before surgery, was 18.9% (27/143). At its worst, pelvic pain was severe for 6.9% (4/58) of patients six months after surgery. Ten out of sixteen patients In Study IV still had pain at a time point 10-44 months after hysterectomy. Nine of those ten patients were considered to be suffering from PPSP. Half of the patients rated their pain as moderate and only one as severe during the week preceding the appointment for clinical examination.

The results of earlier prospective studies of persistent pain after hysterectomy are variable. Pinto et al. reported a 50% prevalence of pain after hysterectomy, mostly performed by the abdominal route (Pinto et al. 2012) and Montes et al. reported a 25% prevalence after abdominal and an 11.8% prevalence after vaginal hysterectomy (Montes et al. 2015). Bransborg et al. found that 16.7% of their patients had persistent pelvic pain after hysterectomy (Brandsborg et al. 2009) but in that study only pain affecting daily living was reported as persistent pain. Most of that persistent pain four months after hysterectomy was regarded as a continuum of pain before hysterectomy and surgery itself was reported to have only a minor contribution. The intensity of pain in Study III, mild in most of the patients, is consistent with earlier reports (Brandsborg et al. 2009; Pinto et al. 2012; Montes et al. 2015).

6.2.2 Predictors for persistent postsurgical pain

The results of Study III indicate a significant association between smoking, severe acute pain and laparoscopy and persistent pelvic pain six months after hysterectomy. The most significant association appears between smoking and persistent pain.

Animal studies have shown that nicotine produces antinociception (Aceto et al. 1983). Mishriky et al. in their recent systematic review and meta-analysis found that administration of nicotine for non-smokers was associated with decreased consumption of opioid in the acute postoperative phase than was the case with controls (Mishriky et al. 2014). In spite of this apparent antinociceptive effect of nicotine, smokers are known to have more chronic pain conditions than non-smokers, e.g. chronic back pain and pelvic pain (Latthe et al. 2006; Pisinger et al. 2011). Yet a large-scale prospective study of breast cancer surgery found no significant association between smoking and PPSP (Meretoja et al. 2014). It has been proposed that the effect of smoking on persistent pain may be explained

through factors other than smoking itself. A study of patients at a multidisciplinary pain clinic found depressive symptoms to be a critical mediating factor in the relationship between smoking and pain (Goesling et al. 2012). In the present study no data on depressive symptoms was elicited, and therefore it was not possible to test the relationship.

Several earlier studies have shown that severe acute pain is a risk factor for persistent postsurgical pain (VanDenKerkhof et al. 2012; Bruce et al. 2014). Also, preoperative pain predicts persistent pain (Niraj and Rowbotham 2011; Meretoja et al. 2014). In line with earlier studies, in Study III severe acute pain was significantly associated with persistent pain. Although the association between preoperative pain and persistent pain was not significant in the multivariable model, the association was significant in the univariate analysis.

Laparoscopic technique has been thought to reduce the incidence of PPSP compared with open technique (Kehlet et al. 2006; Kehlet et al. 2013). Surgical techniques had no effect on the prevalence of persistent pain comparing abdominal hysterectomy to vaginal hysterectomy in earlier studies by Brandborg et al. The laparoscopic approach to hysterectomy was not involved in the studies (Brandsborg et al. 2007; Brandsborg et al. 2009). In another study it was found that abdominal hysterectomy and Phannenstiel incision were significantly associated with persistent pain (Pinto et al. 2012) whereas in a study of major elective gynaecological surgery no association between the type of surgery and persistent postsurgical pain was reported (VanDenKerkhof et al. 2012). In these studies laparoscopic hysterectomy technique was only rarely used. In Study III, on the other hand, patients undergoing abdominal hysterectomy were not included.

Slightly surprisingly, in the present study laparoscopy was significantly associated with persistent pain although acute postoperative pain was shown to be more severe after vaginal hysterectomy in Study II. Long duration of surgery has been shown to increase persistent postsurgical pain (Peters et al 2007). The laparoscopic approach to hysterectomy is known to take significantly longer than does the use of the vaginal technique (Candiani et al. 2009; Sesti et al. 2014) as also clearly shown in Study III. This could be one factor contributing to the increased persistent pain in the laparoscopic group. Unfortunately, duration of surgery was not involved in the logistic regression analysis of Study III. Another explanation could be the number of complications. There were more complications in the laparoscopic group. However, the association between complications and persistent pain did not achieve statistical significance in a multivariate model. Most of the complications were postoperative haematomas and infections, while severe

intraoperative complications, such as ureter injury and occlusion, were seen only in the laparoscopic group. However, in Study IV only three out of sixteen patients had perioperative complications and one of them no longer had pain at the clinical examination. This suggests that complications are not the only cause of the increased prevalence of persistent pelvic pain after laparoscopic hysterectomy.

It has been suggested that anaesthetics may affect the prevalence of PPSP (Song et al. 2012; Cho et al. 2013; Ogurlu et al. 2014). The results of Study III do not support this. Instead, no association between anaesthetic and persistent pain was found in this study. However, it is noteworthy that power analyses before data collection were performed only in the study by Song et al.

6.2.3 Characteristics of persistent pain after hysterectomy

In Study IV persistent pain after hysterectomy was assessed to be of the probable neuropathic type in five and of the possible neuropathic type in three patients. In their recent prospective study, Montes et al. reported a 24% incidence of neuropathic pain after vaginal, and a 44% incidence after abdominal hysterectomy (Montes A et al. 2015). The proportion of neuropathic persistent postsurgical pain has been estimated to be 61% among patients having PPSP after caesarean section (Dualé et al. 2014) and 31-45% after hernia surgery (Haroutiunian et al. 2013). The result of the present study confirms that the mechanisms underlying persistent postsurgical pain are various, also after laparoscopic hysterectomy.

6.3 Health related quality of life

It was shown in Study IV that persistent pain after hysterectomy has consequences for the patient´s health related quality of life, as assessed with the SF-36. This is consistent with the findings on earlier studies of persistent pain after herniotomy and thoracotomy (Kalliomäki et al. 2009; Kinney et al. 2012). In the present study lower scores were found on all scales compared with the results of a Finnish general female cohort study (Aalto et al. 1999). However, studies on all women undergoing hysterectomy for benign causes have shown that hysterectomy improves HRQoL compared to the perioperative situation (Heliovaara-Peippo S et

al. 2013; Kuppermann M et al. 2013). The patients in Study IV patients did not complete the SF-36 before hysterectomy, so it was not possible to compare pre- and postoperative scores.

6.4 Clinical aspects of pain after hysterectomy

The studies of this thesis showed that surgical technique has consequences for the severity of acute postoperative pain but also that the individual variation in the perception of pain is enormous. Severe acute pain is a known predictor for persistent postsurgical pain and this was also shown in Study III. Study IV showed that most of the patients suffering from persistent pelvic pain had no other reason for their pain than their posthysterectomy state and that a large portion of this persistent pain is neuropathic.

In order to prevent pain from becoming persistent individual pain management in the acute postoperative phase is essential. Those patients at elevated risk for severe acute pain and PPSP should be provided with multimodal pain management including psychological interventions. If pain persists, the pain management should be based on the nature of the pain.

6.5 Strengths and weaknesses of the studies

This was a prospective one-centre study of 242 patients who had undergone vaginal or laparoscopic hysterectomy. The study period was from preoperative appointment to a time point six months after surgery for all study patients. In addition, sixteen patients participated in the last part of the study 10-44 months after hysterectomy. All patients had the same acute pain management and assessment protocol. These are the strengths of the study. Study I was a large-scale, blinded, randomized trial. Study II was a large-scale study with a strict pain management protocol. Although it was not randomized, it was a powered study having pain as the primary endpoint, while other studies of this field had pain only as a secondary outcome. The strength of Study III was, in addition to the uniform acute pain protocol, the good response rate (94%).

The first limitation of the thesis is that abdominal hysterectomies were not included. The aim of the first study was to compare two anaesthetics, so only laparoscopic hysterectomies were included. The aim of the second study was to

compare two minimally invasive techniques, vaginal and laparoscopic. Study III was a follow-up study of Studies I and II. As regards persistent pain after hysterectomy, it would have been more informative to have a group of abdominal hysterectomies in this part of the study.

The second limitation was that the vaginal and laparoscopic study groups were not randomized. The surgical approach to performing each hysterectomy was decided by a surgeon. It is known that surgeons' own preferences and local practice may influence the decisions made, so it would be a challenge to randomize patients to different surgical groups.

The limitation of Study IV was a low participation rate (29%). A further limitation was that the timing of the clinical examination ranged from 10 months to 44 months.

6.6 Future prospects

Acute postoperative pain is still undermanaged despite growing knowledge of the mechanism and predictors of severe pain and improved opportunities to treat it. The most significant factors associated with severe postoperative pain, such as psychological factors, type of surgery and preoperative persistent pain, could be identified prior to surgery. In order to achieve better pain management for all surgical patients, we should endeavour to identify these most vulnerable patients preoperatively. Nowadays anaesthetists are able to meet only a fraction of their patients before surgery. Hence what is needed is a validated risk factor measurement tool easy to use in clinical practice. This would enable us to take advantage of all the available pharmacological and psychological tools to prevent and treat postoperative pain.

Persistent pain is a condition with not only individual but also economic and social consequences. The knowledge of predictors associated with persistent postoperative pain is growing. Numerous studies have demonstrated that severe acute pain increases the risk of persistent pain and that psychological factors play an important role in persistent pain. In the present study smoking was the most significant factor for persistent pelvic pain. Smoking is known to increase the risk of postoperative infection and delay wound healing after surgery (Lewin et al. 2014; Bettin et al. 2015). Further clinical studies are needed to ascertain if this prolonged tissue inflammation due to smoking is associated with persistent postsurgical pain.

The best way to decrease postsurgical persistent pain will be the development of novel techniques to avoid surgery. Actually, this has already happened in gynaecological surgery for benign causes. In Finland, the number of hysterectomies has decreased because of better non-surgical treatment (Mäkinen et al. 2013). If surgery is needed, preoperative evaluation of risk for persistent pain is essential. Better methods for persistent pain prevention will be required for patients at elevated risk and therefore large-scale clinical trials will be needed to test possible candidates for preventive drugs and psychological interventions.

The specific mechanisms through which acute pain becomes persistent pain are not yet known. Neuroinflammation and glial cell activation have been implicated in the phenomena. Further studies in this field will yield a better understanding and hopefully new options to prevent and manage chronic pain. The impact of genetics on pain sensitivity and the extent of the effect of genetics on the maintenance of pain is unclear. A growing research area, epigenetics, is the study of processes that lead to heritable modifications in gene function that do not require any concomitant DNA sequence changes (Denk and McMahon 2012). Epigenetics may yield some novel information on the mechanisms involved in the development of persistent postoperative pain. The importance of epigenetic mechanisms in chronic inflammatory and nerve injury pain states remains to be seen.

7 CONCLUSIONS

1. This study shows that the choice of maintaining anaesthesia with propofol or with sevoflurane has no impact on the severity of postoperative pain and the cumulative consumption of opioid after laparoscopic hysterectomy.

2. Patients seem to have less pain and need less rescue opioid after laparoscopic hysterectomy than after vaginal hysterectomy in the acute postoperative phase.

3. Persistent pelvic pain is a common problem six months after laparoscopic or vaginal hysterectomy.

4. The intensity of persistent pain is mild for most patients and pain interferes only slightly with daily activities. Smoking seems to be the most significant predictor for persistent pelvic pain after laparoscopic or vaginal hysterectomy. Other predictors are severe acute pain and laparoscopy.

5. Persistent pain after hysterectomy is neuropathic only in some patients. This suggests that there are mixed pathogenic mechanisms involved in the development of persistent pain after hysterectomy.

6. Persistent pain has an impact on patients´ health related quality of life.

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10 APPENDIX

Number: _____

This questionnaire contains questions, which we ask you to answer by circling the appropriate number below the question, or by writing the answer in your own words.

Date: _____

1. How long did you experience pain after the operation?

1 I don't remember
2 Less than 1 month
3 1 to 3 months
4 Over 3 months, but not anymore
5 I still experience pain

2. If you no longer experience post-operation pain, in the past six months have you felt pain in the pelvic area that has started after you had the operation?

1 Yes
2 No If no, please proceed to Question 13

3. Please describe the pain in your pelvic area.

1 Incessant, constant
2 Incessant, varying in strength
3 Daily bouts of pain
4 Weekly bouts of pain, but not daily
5 Occurs less that once a week

4. Where do you experience the pain?

1 In the middle of the lower abdomen
2 In the vagina
3 In the groin
4 In the lower back
5 Around the operation scar

Elsewhere (Please specify): _____

5. Which of the following best describes the pain (Please circle all appropriate alternatives)?

1 Ache
2 Tenderness
3 Burning sensation
4 Other (Please specify) _____

6. At this moment, how would you score your pain on the scale below? (0 = no pain and 10 = the worst imaginable pain)

0 1 2 3 4 5 6 7 8 9 10
No pain The worst imaginable pain

7. On the scale below, during the past week what is the average amount of pain you had?

0 1 2 3 4 5 6 7 8 9 10
No pain The worst imaginable pain

8. On the scale below, during the past week what was the worst pain you had?

0 1 2 3 4 5 6 7 8 9 10
No pain The worst imaginable pain

9. Does the pain interfere with your sleep?

1 Yes
2 No

10. Do you take any painkillers for your pelvic area pain?

1 Yes (Please specify) _____
2 No

11. Has your pain been treated with by other treatments than painkillers/medicines, such as local anesthesia, physiotherapy etc.? If yes, please specify.

_____

_____

12. Does the pain interfere with your daily activities?

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

13. Other than the pain your pelvic area, do you experience any other pain?

1 Yes
2 No

If yes, please specify: _____

_____

_____

14. Which of the following best describes you at this time?

1 Working full-time
2 Working part-time
3 On a leave of absence
4 Unemployed or laid off
5 On a sick leave
6 Retired or on a rehabilitation grant
7 Studying
8 Other (Please specify) _____

THANK YOU FOR YOUR TIME!

11 ORIGINAL PUBLICATIONS

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The effects of propofol vs. sevoflurane on post-operative pain and need of opioid

S. M. Pokkinen[1], A. Yli-Hankala[1,2] and M.-L. Kalliomäki[1]
[1]*Department of Anaesthesia, Tampere University Hospital, Tampere, Finland and* [2]*Medical School, University of Tampere, Tampere, Finland*

Background: Post-operative pain continues to be a major problem. Some previous studies have suggested that patients anaesthetised with propofol have less pain after surgery than those anesthetised with volatiles. However, the results of previous studies are conflicting. We designed a large-scale trial to study, whether propofol or sevoflurane is more analgesic than the other. We measured opioid consumption in the acute post-operative phase after laparoscopic hysterectomy.
Methods: In a randomised, prospective single-blind trial, we evaluated the consumption of oxycodone and pain intensity in 148 women for 20 h after laparoscopic hysterectomy under propofol or sevoflurane anaesthesia. The primary endpoint was the cumulative amount of oxycodone consumed. Secondary endpoints were pain scores [numeric rating scale (NRS)] at rest and with coughing, severity of nausea and state of sedation.
Results: The consumption of oxycodone and the NRS pain scores did not differ between the groups. The oxycodone consumed during first 20 h after surgery was 42.5 (95% confidence interval 38.3–46.6) mg and 42.8 (37.3–48.4) mg in propofol- and sevoflurane-anaesthetised patients, respectively ($P = 0.919$). NRS scores for nausea were higher in the patients receiving sevoflurane during the first 60 min in the post-anaesthesia care unit, leading to higher consumption of rescue antiemetics. Sedation scores differed in favour of sevoflurane only at 4 h time point after anaesthesia. Patient characteristics did not differ.
Conclusions: In this study, comparing sevoflurane with propofol for maintenance of general anaesthesia, the choice of anaesthetic had no effect on the requirement of oxycodone or intensity of pain after surgery.

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The management of acute post-operative pain is still challenging, despite recent advances in post-operative pain therapy.[1] It is well known that the intravenous anaesthetic propofol has advantages over volatile anaesthetics in the early post-operative period, especially for its antiemetic activity.[2,3] During the last few years, the possible impact of chosen pharmaceuticals, i.e. inhaled anaesthetics vs. propofol, on the severity of post-operative pain has been discussed.[4–6]

The results of the previous investigations have been conflicting.[7] Most of the previous studies have included relatively small number of patients. Some of them have used pain intensity, instead of opioid consumption as their primary outcome measurement, or compared longer-acting isoflurane with short-acting propofol. Therefore, the issue, i.e. the possible effect of used anaesthetic on the need of opioid to cure post-operative pain, remains unclear. We designed an adequately powered, larger scale randomised, prospective, single-blinded study, comparing the analgesic characteristics of propofol to those of sevoflurane. Sevoflurane was chosen to be compared with propofol, since it is a relatively short-acting, commonly used volatile anaesthetic agent. Our primary outcome measurement was the consumption of opioid after laparoscopic hysterectomy. Our secondary outcome measurements were pain intensity, the incidence of nausea and the level of sedation.

Our primary hypothesis was that patients in the propofol group would consume less rescue opioids post-operatively. Secondary hypotheses were that patients receiving propofol as their main anaesthetic would score less in numeric rating scale (NRS) in both level of pain and nausea, and appear less sedated post-operatively.

Methods

Written informed consent was obtained from 168 Finnish-speaking women, who were scheduled for

Trial registry number: Clinical Trials NCT01437462

laparoscopic hysterectomy with or without salpingo-oophorectomy for non-malignant conditions at Tampere University Hospital or Valkeakoski Regional Hospital. The study design was approved by the local Ethics Committee, Pirkanmaa Hospital District, Science Center PO Box 2000, FI-33521 Tampere, Finland, number R08031M, approval date 11 March 2008 and the National Agency of Medicines, and registered with EUDRACT (2008-001125-34) and Clinical Trials (NCT01437462). The inclusion criteria were age < 70 years, American Society of Anesthesiologists (ASA) physical status I/II/III and body mass index < 35 kg/m^2. The exclusion criteria were diabetes, liver disease, present use of opioids or allergies to any of the study medications.

After the enrolment, the patients were randomly assigned into one of the two study groups using a computer-generated random number table by the primary investigator (S. Pokkinen). The patients were anaesthetised either with intravenous (IV) propofol (group P) or with sevoflurane (group S). The patients were blinded to the group allocation.

The study patients were premedicated with per oral midazolam 7.5 mg and cetirizine 10 mg. In the operating room, standard monitoring was started. In group P, anaesthesia was induced and maintained using a target-controlled infusion (TCI: Asena PK, Alaris Medical Systems, Basingstoke, UK; Orchestra Base Primea, Fresenius Vial, Le Grand Chemin, Brezins, France; or B Braun Perfuser Space, B Braun Meisungen AG, Germany) of propofol and remifentanil. In group S, anaesthesia was induced with IV propofol 2–3 mg/kg and maintained with sevoflurane and TCI of remifentanil. Pharmacokinetic model of Schnider[8] was used for administration of propofol (Group P) and that of Minto[9] for administration of remifentanil in both groups. Tracheal intubation was facilitated with rocuronium 0.6 mg/kg and the lungs of the patients were mechanically ventilated with 50% of oxygen in air, unless the individual requirements differed. The delivery of anaesthetics was adjusted to maintain non-invasive arterial blood pressure and heart rate at ± 20% of baseline, and State Entropy (Entropy, GE Healthcare, Helsinki, Finland) below 60. The target concentration of remifentanil was 3–5 ng/ml. To prevent post-operative nausea and vomiting (PONV), all patients received IV dexamethasone 5 mg immediately after induction of anaesthesia. At the end of surgery, all patients were given IV acetaminophen 1 g. When the surgery was completed, the remifentanil infusion was discontinued and IV bolus of fentanyl 0.05 mg was given. Neostigmine 2.5 mg with glycopyrrolate 0.5 mg IV was used to reverse neuromuscular blockade. The total amounts of infused remifentanil and propofol were recorded.

In the post-anaesthesia care unit (PACU), post-operative pain was treated with patient-controlled analgesia (PCA; Abbott Pain Management Provider, Abbott Laboratories, North Chicago, IL, USA, or CADD Legacy PCA, Smiths Medical MD, Inc., St. Paul, MN, USA) with oxycodone 1 mg/ml, using oxycodone bolus doses of 2 mg and a lockout time of 10 min. The patients were informed beforehand of the PCA method in the pre-anaesthetic appointment. As soon as the patients were alert enough to use the PCA device, they were instructed to use it. In addition to the PCA, the rescue pain medication in the PACU was IV bolus of oxycodone 3 mg, if the pain was rated > 3 on NRS pain scores (11-point NRS 0–10) by the patient. The rescue medication was given by the nurses in the PACU, if needed when the patient was not yet alert enough, or if pain medication was needed in addition to the PCA, which had the lockout time of 10 min. During the ward stay, the PCA was continued at least for 20 h after surgery and IV acetaminophen 1 g was administered every 6 h. Rescue opioids were not given by the nurses during the ward stay. Instead, the patients were instructed to press the PCA in case of emerging pain. In case of nausea, the patients were given either a bolus of IV ondansetron 4 mg, or IV droperidol 0.75 mg, if needed. Data were collected for 20 h after patients' arrival at PACU by the nurses in the PACU and by the nurses on the ward. The time of arrival at PACU was registered as time point 0. At time points 0, 10 min, 20 min, 30 min, 60 min, 120 min, 4 h, 6 h, 20 h, the following data were collected: the cumulative amount of oxycodone, NRS pain scores at rest and with coughing, NRS scores (scale 0–10) for nausea, number of episodes of post-operative vomiting and sedation scores measured with a 4-point scale (0 = fully awake; 1 = awaked but still sedated; 2 = asleep but wakes to verbal command; 3 = unresponsive). The need for antiemetic medication was recorded.

Statistical analysis

The sample size estimation was based on the results of a previous study of laparoscopic hysterectomies, where the mean consumption of oxycodone was 0.45 [standard deviation (SD) 0.24] mg/kg during the first 24 post-operative hours,[10] indicating a need of 75 patients per group to show a 25% intergroup difference with power of 0.8 and α of 0.05. The dif-

ference of 25% was chosen, because it was considered as a clinically meaningful decrease in the total consumption of opioid.

Data on patients' age, weight, height, duration of anaesthesia and surgery, intraoperative remifentanil consumption and infusion rate were analysed using independent sample *t*-test. NRS scores for pain and nausea and cumulative oxycodone consumption were compared using an analysis of variance for repeated measures. For *post hoc* comparisons, we used independent sample *t*-test, as needed. ASA classifications and sedation were compared using Mann–Whitney test, and smoking habits, types of surgery and the number of doses of rescue antiemetics with a χ^2 test. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS), Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The study was carried out during the period of October 2008 and March 2013. All 168 consenting women were randomised into the study. The final analysis consisted of 74 patients in each group (Fig. 1). In one patient of both groups, PCA medication was terminated early, and their data were withdrawn from the analyses. One patient in sevoflurane group was given per oral ibuprofen 600 mg for headache 3 h after surgery, but her data were included in the analyses. Another patient in propofol group underwent re-laparoscopy 14 h after the first operation. Her data were used up to six post-operative hours. Characteristics of patients and surgery are presented in Table 1.

Our primary hypothesis was rejected. The cumulative consumption of oxycodone did not differ between propofol anaesthetised and sevoflurane anaesthetised patients at any measure point (Fig. 2).

Regarding our secondary hypotheses, the NRS pain scores at rest and with coughing were similar between the groups (Fig. 3); the nausea scores and consumption of antiemetics were lower in the propofol group during the first hour after anaesthesia; and the sedation scores were equal in most of the measurement points.

The mean NRS scores for nausea during the time 10–60 min after surgery were 0.03–0.24 in propofol group, compared with 0.69–1.53 in sevoflurane group ($P < 0.01$). Thereafter, the groups did not differ, and the mean NRS scores were under 0.49. The requirement of antiemetics (median 0, lower quartile Q_1–upper quartile Q_3 0–1) was higher in sevoflurane group than in propofol group (median 0, Q_1–Q_3 0-0) ($P = 0.018$). The sedation scores were similar in both groups during PACU stay, and 6 and 20 h after surgery. At the time point 4 h after surgery, the sedation scores were higher (median 0,

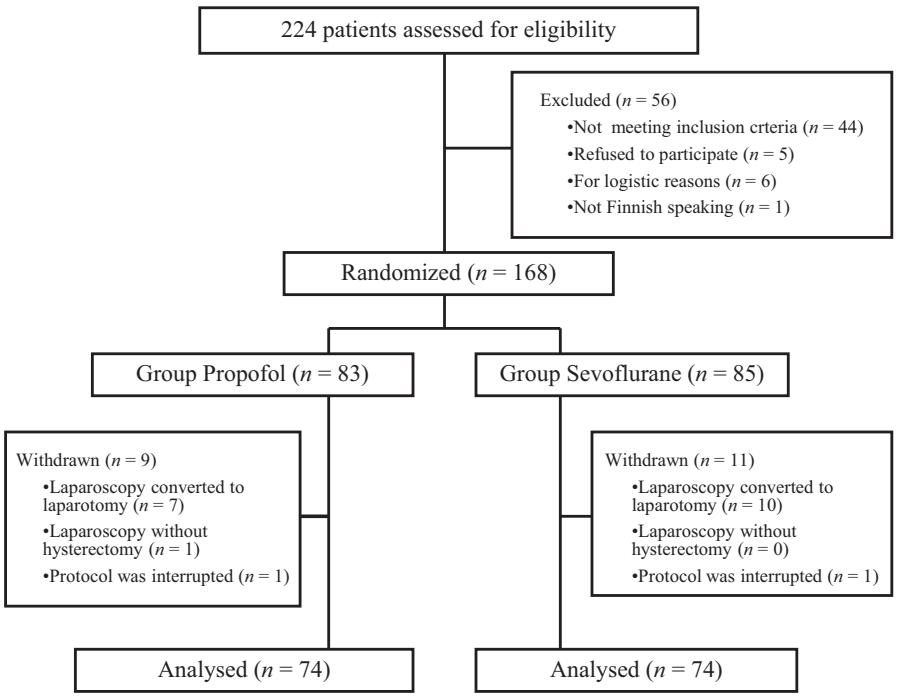

Fig. 1. Flowchart of the patients.

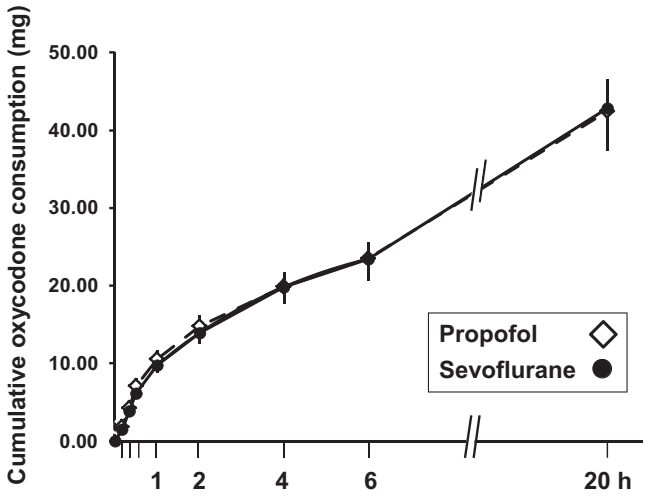

Fig. 2. Cumulative consumption of oxycodone [mean, 95% confidence interval (CI)] in patients anaesthetised with propofol (dashed line) or with sevoflurane (solid line) during the 20 h after surgery. No significant differences.

Table 1

Characteristics of patients and surgery.

	Propofol ($n = 74$)	Sevoflurane ($n = 74$)
Age (year)	50.2 (7.2)	50.6 (7.9)
Weight (kg)	70.7 (12.2)	70.0 (10.9)
Height (cm)	165.8 (6.0)	165.2 (5.5)
Smoking	10 (13.5)	11 (14.9)
Type of surgery		
LH	32 (43.2)	36 (48.6)
LH with salpingo-oophorectomy	42 (56.8)	38 (51.4)
Duration of anaesthesia (min)	169.9 (44.0)	172.3 (39.6)
Duration of surgery (min)	136.0 (44.3)	136.2 (40.8)

Values are mean (SD) or *n* (%).
LH, laparoscopic hysterectomy.

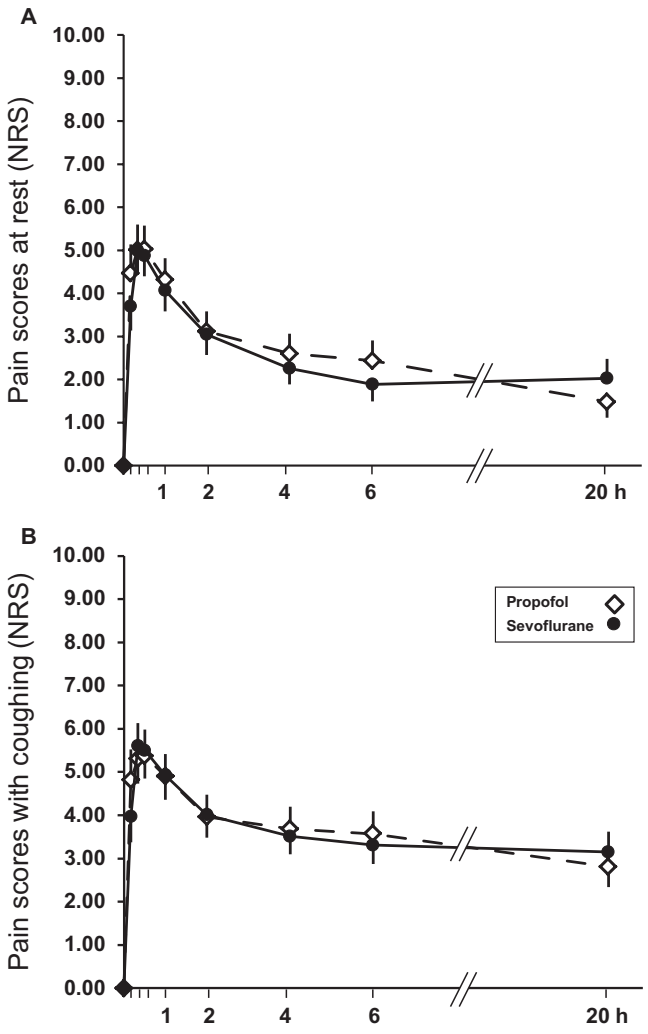

Fig. 3. NRS pain scores (mean, 95% CI) (A) at rest and (B) with coughing in patients anaesthetised with propofol (dashed line) or with sevoflurane (solid line) during the 20 h after surgery. No significant differences.

Q_1–Q_3 0–1) in propofol group compared with scores (median 0, Q_1–Q_3 0-0) in sevoflurane group ($P = 0.039$). Because 69% of the study patients in both groups were deeply sedated at time point 0, we decided to start the analyses at time point 10 min after the patients arrived at PACU. Total intraoperative consumption of remifentanil did not differ between the groups. In propofol group, the mean total dose of remifentanil was 1446.5 (SD 471.8) mcg. In sevoflurane group, the mean dose was 1312.8 (393.5) mcg ($P = 0.063$). Mean infusion rates of remifentanil for the patients receiving propofol and for those anaesthetised with sevoflurane were 0.12 (0.02) and 0.11 (0.02) mcg/kg/min, respectively ($P < 0.001$).

Discussion

The results of our study did not show any difference in requirements of analgesics, or in the intensity of post-operative pain, after propofol-remifentanil-air/O_2 or sevoflurane-remifentanil-air/O_2 anaesthesia over the 20 h following period in females scheduled for gynaecological surgery. Our findings are in line with the previous study of Fassoulaki et al., which showed no influence of sevoflurane, desflurane or propofol anaesthesia on analgesic requirement or pain.[5] The results of our study do not support earlier results of clinical association between general anaesthetics and post-operative pain.[4,6,11–13]

Possible explanations for these deviations are differences in the sample size estimations, in primary

outcome measurements and in the study protocols between the investigations. The value of using analgesic consumption, instead of pain scores, as the primary outcome measurement has been acknowledged.[14]

In clinical situations, the intensity of pain depends on many different factors, including nociception and central sensitisation mechanisms. Also patient-related factors, like genetics, mood and psychosomatics, often contribute. It has also been shown that isoflurane is hyperalgesic at low concentrations and analgesic at high concentrations.[15,16] On the other hand, the effects of propofol on analgesia and hyperalgesia have been studied in healthy volunteers; it seems to induce analgesia and antihyperalgesia, but the effects disappear shortly after cessation of the infusion.[17] Furthermore, remifentanil-induced post-infusion hyperalgesia is not completely antagonised by propofol.[18]

The role of opioids and especially the ultra short-acting opioid remifentanil appears to be more important, for the development of acute post-operative pain. There is some evidence that opioid-induced hyperalgesia (OIH) and opioid tolerance may develop also after acute perioperative use of opioids and mainly after remifentanil-based anaesthesia. The development of OIH seems to be dose related and results in more severe pain and increased opioid consumption after surgery.[19–23] In our study, the intraoperative administration of remifentanil was controlled and the cumulative consumption was similar between study groups. Although the mean remifentanil infusion rates differed between groups, the doses were low[21,24,25] and the difference was minor; thus, most probably not contributing the results obtained.

The choice of general anaesthetic contributes to the incidence of post-operative nausea, as shown before[3] and also in our study. Although propofol did not decrease the incidence of pain after laparoscopic hysterectomy, it diminished nausea during the first hour after surgery.

Our study has some limitations. First, the study was designed as a single-blinded trial, i.e. the nursing staff collecting the data was not blinded for the used anaesthetic. In our experience, however, it is impossible to blind the PACU nurse when volatile anaesthetics are used. In our experience, breath odour of the patient would immediately reveal the use of volatile anaesthetic upon arrival to PACU. Furthermore, we used the consumption of oxycodone, and not the pain scores, as our primary outcome measurement. The patient herself administered oxycodone as soon as she was able to do so, typically within 30 min already in the PACU. Therefore, we suppose that the lack of blinding had no significant influence to the results. Second, the study was not a pure comparison between propofol and sevoflurane anaesthesia, as all patients were given propofol during induction of anaesthesia. Because inhaled induction with sevoflurane is not a common practice with adult patients, it was not used in this study, either. Although the total duration of anaesthesia (170 min) most probably outlasted any potential effects of propofol, it is possible that propofol had some influence on the results. The choice of a third anaesthetic as an induction agent might have been the solution to make the groups more comparable. Nevertheless, we consider our use of propofol to be relevant clinical practice. Third, the mean remifentanil infusion rates between the groups differed, but the infusion rates were low in both groups and the difference was judged clinically irrelevant. Lastly, the time of discharge from the PACU to the ward was not registered. In a clinical setting, such as ours, this would not be of relevance, since the discharge is dependent of both patient-related factors (which would be informative for the study) and administrative issues (not informative for the study). In any case, patients stayed in the PACU long enough to be able to use the PCA already in the PACU, rendering them independent of the rescue medication given by a nurse.

In conclusion, we did not find differences in the requirement of oxycodone or severity of acute pain after laparoscopic hysterectomy for non-malignant conditions between patients who had received propofol or sevoflurane for the maintenance of their anaesthesia. Although general anaesthetics have some effects on nociception and pain modulation, the significance of the choice of anaesthetic seems to be meaningless for acute pain after surgery. Obviously, the mechanisms of general anaesthetics on the pain pathway remain unclear and need more basic research, with controlled study settings, using clinically comparable concentrations of anaesthetics.

Conflicts of interest: The authors have no conflicts of interest.

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Address:
Satu Pokkinen
Department of Anaesthesia
Tampere University Hospital
PO Box 2000
FI-33521 Tampere
Finland
e-mail: satu.pokkinen@pshp.fi

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GENERAL GYNECOLOGY

Less postoperative pain after laparoscopic hysterectomy than after vaginal hysterectomy

Satu M. Pokkinen · Maija-Liisa Kalliomäki · Arvi Yli-Hankala · Kari Nieminen

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Abstract
Purpose To find out whether the severity of acute postoperative pain differs between laparoscopic (LH) or laparoscopically assisted vaginal hysterectomy (LAVH) and vaginal hysterectomy.
Methods In a prospective, powered, non-randomized trial, the consumption of oxycodone and pain scores were evaluated in 164 women up to 20 h after VH or LH/LAVH. All hysterectomies were performed under standardized general anesthesia and the pain medication was similar in both groups. The primary endpoint was the cumulative oxycodone consumed. Main secondary endpoints were pain scores (numeric rating scale NRS), operative time and hospital stay.
Results The patients in LH/LAHV group consumed less opioid than the patients in the vaginal group during the 20 h period after surgery. The difference was significant at time point 4 and 6 h. The oxycodone consumed at time point 4 h was 19.9 (95 % CI 18.1–21.7) mg in laparoscopic group and 22.8 (20.7–25.0) mg in vaginal group ($p = 0.040$) and at time point 6 h was 23.5 (21.5–25.6) mg in laparoscopic group and 27.4 (24.7–30.0) mg in vaginal group ($p = 0.026$). Pain scores were lower after laparoscopic approach and the difference was significant at time point 60 min after surgery ($p = 0.026$).
Conclusion In this study, LH was associated with reduced need of analgesics and lower acute postoperative pain scores than VH.

Keywords Postoperative pain · Hysterectomy · Vaginal · Laparoscopy · Analgesics

Introduction

Hysterectomy is one of the most common surgical operations for benign causes. Earlier studies have shown that recovery after laparoscopic (LH) or vaginal (VH) hysterectomy is faster than after the abdominal (AH) approach [1, 2]. The laparoscopic technique takes a little longer time than the vaginal technique [1, 3–6] but it offers the advantage of viewing the intra-abdominal status and alleviates performing salpingo-oophorectomy [5, 7]. Regardless of many studies comparing different routes, the choice of route still depends on the surgeon's experience and on local preferences [2, 8]. The Cochrane review of 34 trials and American College of Obstetricians and Gynecologist (ACOG) committee opinion No 444 concluded that VH should be performed in preference to AH and where VH is not possible, LH has some advantage over AH [9, 10].

The management of acute postoperative pain is still challenging despite advances in postoperative pain therapy [11]. Inadequate treatment of severe acute pain results in suffering and prolonged recovery and it has been identified as a risk factor for persistent postsurgical pain [12] thus rendering a considerable impact on the costs at society level [13].

S. M. Pokkinen (✉) · M.-L. Kalliomäki · A. Yli-Hankala
Department of Anesthesia, Tampere University Hospital, PO Box 2000, 33521 Tampere, Finland
e-mail: satu.pokkinen@pshp.fi

A. Yli-Hankala
Medical School, University of Tampere, Tampere, Finland

K. Nieminen
Department of Obstetrics and Gynecology, Tampere University Hospital, PO Box 2000, 33521 Tampere, Finland

There are only a few trials comparing postoperative pain scores or consumption of analgesics between patients who underwent LH with patients who underwent VH. In the meta-analysis published in 2011 Gendy et al. [14] concluded that total laparoscopic hysterectomy (TLH) may offer benefits compared with VH. TLH was associated with reduced postoperative pain scores and reduced length of postoperative hospital stay. Do LH and laparoscopically assisted vaginal (LAVH) hysterectomy share the same benefits over VH is unclear.

This study was designed to compare postoperative pain after VH and LH or LAVH hysterectomy for benign causes. The primary outcome was the opioid consumption. Secondary outcomes were pain intensity, operative time, hospital stay, and blood loss.

Materials and methods

The study was carried out during the period October 2008 and March 2013 and a total of 182 women enrolled into the study. We obtained the written informed consent of 99 Finnish-speaking women, who were scheduled for vaginal hysterectomy (VH) with or without salpingo-oophorectomy for non-malignant conditions at Tampere University Hospital or Valkeakoski Regional Hospital. The LH group ($N = 83$) was obtained from our other study conducted simultaneously, comparing two different techniques of anesthesia. In that study the patients, who were scheduled for laparoscopic hysterectomy, were randomized into group propofol anesthesia or sevoflurane anesthesia. The patients who were anesthetized with propofol formed the LH group to the present study. The study design was approved by the Ethics Committee (R09003) and registered with ClinicalTrials.gov (NCT01442961). The inclusion criteria were younger than 70 years, American Society of Anesthesiologists (ASA) physical status classification I/II/III and body mass index <35 kg/m^2. The exclusion criteria were diabetes, liver disease, present use of opioids, uterine prolapse and allergies to any of the study medications.

The type of hysterectomy (AH, LH or VH) was determined by the surgeon's preference before the written informed consent was obtained. The main reason for abdominal hysterectomy was enlarged uterus and these patients were not involved in this study. The route of surgery, laparoscopic or vaginal, was not strictly determined in the protocol.

All operations were performed under general anesthesia. The study patients were premedicated with peroral midazolam 7.5 mg and cetirizine 10 mg. In the operating room, standard monitoring was started. Anesthesia was induced and maintained with a target-controlled infusion of propofol [15] and remifentanil [16]. Tracheal intubation was facilitated with rocuronium, and the patients were mechanically ventilated with mixture of oxygen in air. The delivery of anesthetics was adjusted to maintain non-invasive arterial blood pressure and heart rate at $\pm$20 % of baseline, and State Entropy (Entropy, GE Healthcare, Helsinki, Finland) below 60. To prevent postoperative nausea and vomiting (PONV), all patients were medicated with IV dexamethasone 5 mg immediately after induction of anesthesia. At the end of surgery all patients were given IV paracetamol 1 g. When the surgery was completed, the remifentanil infusion was discontinued and IV bolus of fentanyl 0.05 mg was given. Neostigmine 2.5 mg with glykopyrrolate 0.5 mg IV was given to reverse neuromuscular blockade. The total amounts of infused remifentanil and propofol were recorded.

Surgical techniques

Vaginal hysterectomy (VH)

The technique for VH was briefly as follows. A local anesthetic containing lidocain and epinephrine was injected under the cervical mucosa. A circumferential incision was made and vaginal mucosa was dissected from the cervix. The peritoneal cavity was entered via posterior cul-de-sac. After that the parametrial tissue, uterine vessels, ovarian vessels and fallopian tubes or with patients undergoing salpingo-oophorectomy the infundibulopelvic ligaments were ligated with sutures and the uterus was removed. The vaginal wall was sutured with absorbable continuous suture.

Laparoscopic hysterectomy (LH)

LH group consisted of LH and LAVH. The pneumoperitoneum was created by inserting the Veress needle into the abdominal cavity through umbilicus or in the cases with suspected intra-abdominal adhesions the Hasson's technique was used for entry, a 10 mm trocar was used for camera. Additional three trocars of 5 mm were inserted laterally of both epigastric arteries and in the midline above symphysis. Bipolar forceps for electrocautery were used to create hemostasis. In LH uterine arteries were controlled laparoscopically whereas in LAVH vaginally with sutures. A local anesthetic containing lidocain and epinephrine was injected under the cervical mucosa before the vaginal incision and the uterus was removed through the vagina and the cuff was closed with vaginal continuous suture.

Both VH and LH group included hysterectomies or hysterectomies with oophorectomy.

In the post anesthesia care unit (PACU) postoperative pain was treated with patient-controlled analgesia (PCA) with oxycodone 1 mg/ml using 2 mg bolus of oxycodone

and a lock-out time of 10 min. The rescue pain medication was IV bolus of oxycodone 3 mg, if the pain was rated >3 on NRS pain scores (11-point numeric rating scale where 0 means no pain and 10 means worst pain imaginable) by the patient. During the ward stay the PCA was continued at least for 20 h after surgery and IV paracetamol 1 g was administered every 6 h. In case of nausea, the patients were given either a bolus of IV ondansetron 4 mg, and if needed IV droperidol 0.75 mg.

Data were collected up to 20 h after patients' arrival at PACU. The time the patient arrived at PACU was registered as time point 0. At time points 10 min, 20 min, 30 min, 60 min, 120 min, 4 h, 6 h, 20 h, the following data were collected: the cumulative amount of oxycodone, NRS pain scores at rest and with coughing, NRS scores for nausea, number of episodes of postoperative vomiting and sedation scores measured with a 4-point scale (0 = fully awake; 1 = awaked but still sedated; 2 = asleep but wakes to verbal command; 3 = unresponsive). The need for antiemetic medication was recorded.

Data regarding the patients' characteristics and surgical outcomes were collected from the patients' medical records.

Statistical analysis

The sample size estimation was based on the results of a previous study of laparoscopic hysterectomies, where the mean consumption of oxycodone was 0.45 (SD 0.24) mg/kg^2 during the first 24 postoperative hours [17], indicating a need of 75 patients per group to show 25 % inter-group difference with power of 0.8 and α of 0.05.

Data on patientś age, weight, height, and cumulative oxycodone consumption were analyzed using independent sample *t* test. NRS scores for pain, doses of antiemetic drugs, sedation, duration of surgery, weight of uterus and blood loss were compared using Mann–Whitney test. χ^2-test was used to analyze smoking habits, ASA, NRS scores for nausea, type of surgery, indication of surgery and hospital stay. Probability (p) values <0.05 were considered significant. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS^{TM}), Windows version 20.0 (SPSS Inc.; Chicago, IL., USA).

Results

In the final analysis, there were 90 patients in the VH group and 74 patients in the LH group. The flow of the patients is presented in Fig. 1. One patient in the VH group was given IV ketoprofen 100 mg on the ward and one patient in the LH group underwent relaparoscopy 14 h after the first operation. These patients were included in the final analysis but the second one only up to six postoperative hours. Demographic data of patients are presented in Table 1.

The patients in the LH group consumed less oxycodone after surgery than the patients in the VH group. The difference was significant at time point 4 h ($p = 0.040$) and at time point 6 h ($p = 0.026$) after surgery (Fig. 2). NRS pain scores at rest were significantly lower in the LH group at time point 60 min ($p = 0.026$) after surgery (Fig. 3) as were the NRS scores for nausea. At the time point 60 min 97 % of patients had no nausea in the LH group compared with 84 % of patients in the VH group ($p = 0.002$), however, no difference in the need for antiemetic medication was found ($p = 0.098$). The difference in NRS pain scores with coughing was not significant at any observed time. The recovery from anesthesia was similar in both groups.

The indications of surgery differed partly in VH and LH groups. The most common main indication of surgery in both groups was uterine leiomyoma. In the LH group there were more salpingo-oophorectomies compared with the VH group, the duration of surgery was longer and the patients stayed for a longer time in hospital (Table 2).

Discussion

In our study the laparoscopic technique for hysterectomy was associated with reduced consumption of analgesics in the acute postoperative period compared with the vaginal technique. However, the intensity of pain and the need of analgesics varied considerably between patients.

Most of the studies comparing vaginal and laparoscopic approach have focused on the incidence of perioperative complications, the operative time and the length of hospital stay. To our knowledge only Ghezzi et al. [18] have shown in a randomized prospective trial having postoperative pain as the primary outcome that TLH is associated with lower postoperative pain scores and a reduced need for rescue analgesia compared with the vaginal approach. The findings of our study comparing VH with LH or LAVH are similar with those by Ghezzi et al. despite the difference in technique. In Finland the main technique for laparoscopic hysterectomy is either LH or LAVH and THL is performed rarely [19]. Other studies in the field have discussed pain measurement and management, but it has not been the primary focus of these studies. In the eVALuate trial by Garry et al. [2] a higher proportion of patients undergoing VH used opioids than patients undergoing LH and Soriano et al. [4] reported that the use of analgesics did not differ between LAVH and VH groups.

In our study the consumption of opioids was chosen as for the primary outcome and pain scores as secondary outcome, since ethically both of the groups should be allocated a similar level of analgesia, i.e. adequate pain

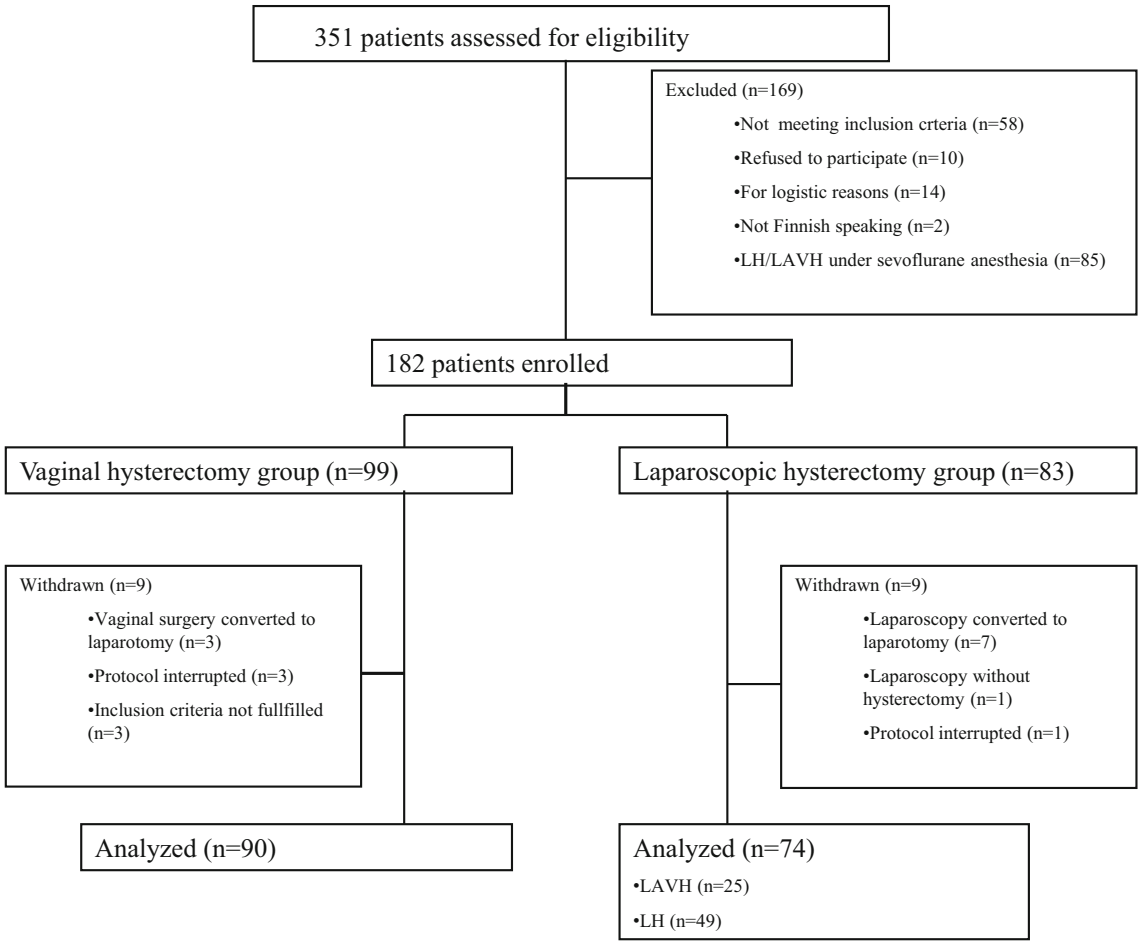

Fig. 1 Flowchart of the patients

Table 1 Demographic data of patients

	VH ($n = 90$)	LH ($n = 74$)	p value
Age (year)	47.5 (6.3)	50.2 (7.2)	0.013
Weight (kg)	71.1 (10.4)	70.7 (12.2)	0.841
Height (cm)	165.9 (4.9)	165.8 (6.0)	0.940
Smoking	24 (26.7 %)	10 (13.5 %)	0.043
Physical status			0.269
ASA 1–2	90 (100.0 %)	73 (98.6 %)	
ASA 3	0 (0.0 %)	1 (1.4 %)	

Values are mean (SD), *n* (%)

VH vaginal hysterectomy, *LH* laparoscopic hysterectomy, *ASA* American Society of Anesthesiologist physical status classification

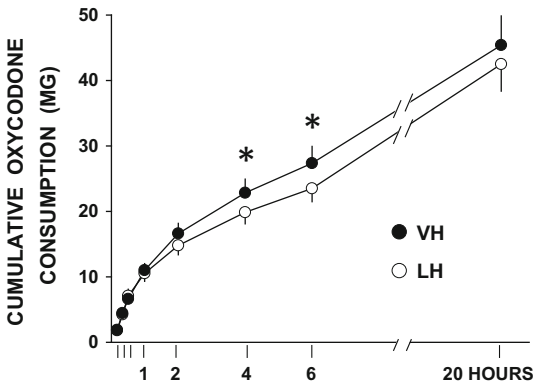

Fig. 2 Cumulative consumption of oxycodone (mean, 95 % CI) in patients who underwent laparoscopic hysterectomy (LH) or vaginal hysterectomy (VH) during the 20 h after surgery. The difference was significant at time point 4 h ($p = 0.040$) and at time point 6 h ($p = 0.026$)

treatment. The patients announced significantly higher pain scores in the postanesthesia care unit 1 h after vaginal surgery than after laparoscopic surgery. The cumulative consumption of oxycodone was increased thereafter in the VH group compared with the LH group although the statistical significance was found only at time points four and 6 h after surgery.

Minimal invasive surgical techniques have been indicated to reduce acute postoperative pain as has been shown in trials comparing abdominal hysterectomies with

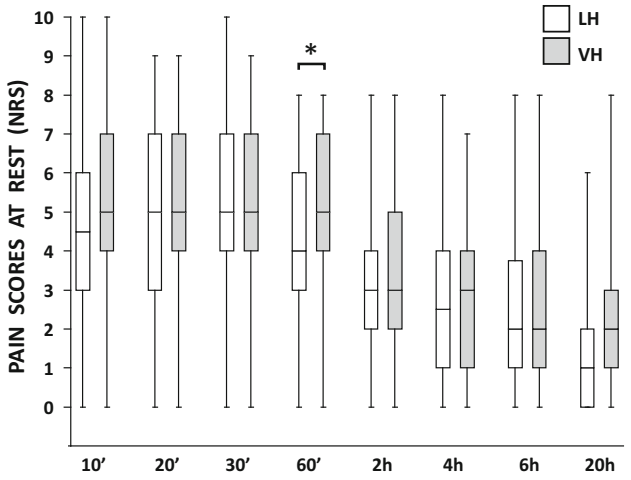

Fig. 3 NRS pain scores (median, 25th and 75th percentile range, minimum, maximum) at rest in patients who underwent laparoscopic hysterectomy (LH) or vaginal hysterectomy (VH) during the 20 h after surgery. The difference was significant at time point 60 min ($p = 0.026$)

laparoscopic hysterectomies [2, 7, 20]. Vaginal hysterectomy has been regarded as the most minimally invasive technique of hysterectomy whereas laparoscopic hysterectomy moderately invasive [21]. Yet, in our study, regardless of more salpingo-oophorectomies and a longer operation time, the patients in laparoscopic group experienced less postoperative pain. The management of bleeding differs between VH and LH and also this might affect the pain intensity. In the laparoscopic route electrocautery is used to create hemostasis whereas vessels are ligated with sutures in the vaginal approach. Even though there are many arguments supporting VH over LH, these findings of pain should not be ignored. In contrast to the findings of meta-analysis by Gendy et al. [14], in our study laparoscopy was associated with a longer hospital stay compared with vaginal hysterectomy. The reason for this is unclear, and could not be found in a retrospective analysis of the medical notes of the patients.

The first limitation of this study is the unexpectedly long enrollment period; the study was a one-site study carried out in Pirkanmaa Hospital District including Tampere University Hospital and Valkeakoski Regional Hospital. In the university hospital setting most of the gynecological patients are cancer patients or otherwise severely ill and the number of patients to be operated for benign causes is minor. The data were collected by the primary investigator, which also made challenges for the enrollment. The technique of surgery was not changed during the study enrollment. Thus, in our consideration the long enrollment period does not influence the results. The second limitation is lack of randomization. Randomization of patients into the study groups would be difficult because of

Table 2 Characteristics of surgery

	VH ($n = 90$)		LH ($n = 74$)		p value
	n	%	n	%	
Main indication of surgery					
Uterine leiomyoma	68	75.6	50	67.6	0.257
Menstrual disorders	15	16.7	13	17.6	0.879
Pelvic pain	6	6.7	3	4.1	0.465
Other	1	1.1	8	10.8	0.007
Type of surgery					
Hysterectomy with SO	6	6.7	42	56.8	<0.001
Hospital stay					<0.001
1 day	81	90	43	59[n]	
2–4 days	9	10	30	41[n]	

	VH ($n = 90$)		LH ($n = 74$)		p value
	Median	Q1–Q3	Median	Q1–Q3	
Duration of surgery (min)	64	46–78	131	104–167	<0.001
Estimated blood loss (ml)	109	50–200	143	50–350	0.338
Uterus weight (g)	216	150–330	200	135–334	0.486

VH vaginal hysterectomy, *LH* laparoscopic hysterectomy, *SO* salpingo-oophorectomy, *Q1* lower quartile, *Q3* upper quartile

[n] $n = 73$ one patient is not included because of relaparoscopy 14 h after the first operation

gynecologists own preferences to surgical routes. To make the groups comparable we excluded all patients with uterine descent. The uterine prolapse is one of the most common cause to choose the vaginal route, whereas the other causes are more dependent on gynecologists own preferences. Although there were some differences in the proportions of indications, the main indication of surgery was uterine leiomyoma in both groups and the weight of uterus was similar between groups.

In conclusion, we found that the LH is associated with less oxycodone use and lower NRS pain scores postoperatively than VH. The intensity of pain and the need of analgesics varied considerably between patients.

Conflict of interest The authors declare that they have no conflict of interest and they have full control of all primary data and agree to allow the journal to review the data if requested. No study sponsors have been involved.

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ORIGINAL ARTICLE

Persistent posthysterectomy pain

A prospective, observational study

Satu M. Pokkinen, Kari Nieminen, Arvi Yli-Hankala and Maija-Liisa Kalliomäki

BACKGROUND There is a large variation in the prevalence of persistent postsurgical pain depending on the type of surgery. It is unclear how common persistent postsurgical pain is after vaginal or laparoscopic hysterectomy.

OBJECTIVES The objective of this study was to define the prevalence of persistent postsurgical pain 6 months after laparoscopic or vaginal hysterectomy for benign causes and to ascertain the intensity of the pain and its possible predictors.

DESING A prospective, observational study.

SETTING Pirkanmaa Hospital District between October 2008 and September 2013.

PATIENTS Two hundred and forty-two women who underwent laparoscopic (150) or vaginal (92) hysterectomy for benign causes and who also participated in our earlier studies concerning acute pain.

INTERVENTIONS A pain questionnaire and a prestamped return envelope were mailed to all women 6 months after surgery. If the questionnaire had not been returned within 4 weeks, a reminder was sent. Data regarding preoperative pain and acute postoperative pain were collected from the records of our earlier studies concerning acute pain. The patient characteristics and surgical outcomes were collected from the patients' medical records.

MAIN OUTCOME MEASURE The prevalence of persistent postsurgical pain 6 months after hysterectomy.

RESULTS The response rate was 94% (227 respondents). Twenty-seven (18.9%) of 143 patients who had no pain preoperatively had persistent pain after surgery. Overall, 26.0% of patients had persistent pelvic pain 6 months after surgery. On an 11-point numeric rating scale (NRS), most of the patients rated their average pain as mild (NRS 0 to 3) and only 6.9% rated their worst pain as severe (NRS 7 to 10). Smoking, acute postoperative pain at 4 h after surgery and a laparoscopic approach were significantly associated with persistent pain in a multivariable analysis.

CONCLUSION Persistent posthysterectomy pain is common, but pain is mild and does not interfere with daily activities for most of the patients 6 months after surgery. Smoking is the strongest predictor for persistent pain.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT 01537731.

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Introduction

Persistent postsurgical pain is defined as pain that persists for at least 2 months after surgery, is not a continuation of a preoperative pain, is located at the site of surgery and cannot be explained by any other cause. The incidence of persistent postsurgical pain varies after different types of surgery, ranging from 10% up to 50% of patients.[1]

Hysterectomy is one of the most common surgical operations for benign causes.[2] It is performed to relieve various symptoms and consequently is expected to result in a better quality of life. Chronic pelvic pain is a common problem in women[3] and often such pain is one of the reasons leading to the decision for hysterectomy. Previous prospective studies have found the prevalence

From the Department of Anaesthesia, Tampere University Hospital (SMP, MLK, AYH), University of Tampere, Medical School (AYH), and the Department of Obstetrics and Gynaecology, Tampere University Hospital, Tampere, Finland (KN)

Correspondence to Satu M. Pokkinen, Department of Anaesthesia, Tampere University Hospital, P.O. Box 2000, Tampere FI-33521, Finland
Tel: +3583311611; fax: +358331164363; e-mail: satu.pokkinen@pshp.fi

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of persistent posthysterectomy pain to be in the region of 14 to 50%. In these studies, most of the patients had undergone abdominal hysterectomy.[4–6] The laparoscopic approach to hysterectomy has only recently become popular and knowledge regarding persistent pain after laparoscopic hysterectomy is sparse.

The aim of this prospective study was to define the prevalence of persistent postsurgical pain 6 months after laparoscopic or vaginal hysterectomy for benign causes. The secondary aim was to note the intensity of the pain and the role of anaesthetic, surgical or patient-related factors in predicting persistent postsurgical pain.

Materials and methods

Ethical approval for this study was provided by the Ethics Committee, Pirkanmaa Hospital District, Tampere, Finland on 9 December 2008 (R08031M) and 13 January 2009 (R09003).

This was a follow-up study of two previous consecutive studies concerning acute pain after laparoscopic or vaginal hysterectomies carried out between October 2008 and March 2013. The results concerning acute pain were reported previously by Pokkinen *et al.*[7,8] Written informed consent was obtained from 267 Finnish speaking women who had been scheduled for laparoscopic or vaginal hysterectomy, with or without salpingo-oophorectomy, for nonmalignant conditions in Pirkanmaa Hospital District, which included Tampere University Hospital and Valkeakoski Regional Hospital. The study was registered with ClinicalTrials.gov (NCT01537731). The inclusion criteria were women younger than 70 years of age with American Society of Anesthesiologists (ASA) status classification I/II/III and BMI less than 35 $kg\,m^{-2}$. Exclusion criteria were diabetes, liver disease, concurrent use of opioids, uterine prolapse and allergies to any of the study medications.

At the preoperative appointment, patients were asked to rate their preoperative pelvic pain on an 11-point numeric rating scale (NRS), both at rest and during movement (0 meant no pain, and 10 meant the worst imaginable pain).

Anaesthesia

The study patients were premedicated with oral midazolam 7.5 mg and cetirizine 10 mg. Anaesthesia was induced and maintained using target-controlled infusions of propofol and remifentanil (TCI: Asena PK, Alaris Medical Systems, Basingstoke, UK; Orchestra Base Primea, Fresenius Vial, Le Grand Chemin, Brezins, France; or B Braun Perfuser Space, B Braun Meisungen AG, Germany), or induced with intravenous (i.v.) propofol 2 to 3 $mg\,kg^{-1}$ and maintained with sevoflurane and a target-controlled infusion of remifentanil. The Schnider pharmacokinetic model[9] was used for administration of propofol (Group P) and the Minto pharmacokinetic model[10] for administration of remifentanil. Tracheal intubation was facilitated with rocuronium and the lungs of the patients were mechanically ventilated with an air/oxygen mixture to deliver a 50% inspired oxygen fraction, unless individual patient requirements dictated otherwise. The delivery of anaesthetics was adjusted to maintain noninvasive arterial blood pressure and heart rate within ±20% of baseline, and state entropy (Entropy; GE Healthcare, Helsinki, Finland) below 60. The target concentration of remifentanil was 3 to 5 $ng\,ml^{-1}$. To prevent postoperative nausea and vomiting (PONV), all patients received prophylactic i.v. dexamethasone (5 mg) immediately after induction of anaesthesia. At the end of surgery, all patients were given i.v. paracetamol 1 g. When the surgery was completed, the remifentanil infusion was discontinued and an i.v. bolus of fentanyl 0.05 mg was given. Intravenous neostigmine 2.5 mg with glycopyrrolate 0.5 mg i.v. was used to reverse neuromuscular blockade. The total amounts of infused remifentanil and propofol were recorded.

Surgery

Vaginal hysterectomy

A local anaesthetic (lidocaine 2.5 $mg\,ml^{-1}$ and epinephrine 5 $\mu g\,ml^{-1}$) was injected under the cervical mucosa. A circumferential incision was made, the peritoneal cavity entered and the parametrial tissue, uterine vessels, ovarian vessels and fallopian tubes (or infundibulopelvic ligaments when appropriate) were ligated and the uterus was removed. The vaginal cuff was sutured with absorbable continuous suture.

Laparoscopic hysterectomy

This group consisted of women who had either laparoscopic or laparoscopically assisted vaginal (LAVH) hysterectomies. For the camera, a 10 mm diameter trocar was inserted into the abdominal cavity through a subumbilical incision. An additional three trocars of 5 mm diameter were inserted, laterally and in the midline above the symphysis pubis. Bipolar forceps was used to create haemostasis. In laparoscopic hysterectomy, the uterine arteries were ligated via the laparoscope, whereas in LAVH, they were ligated transvaginally. A local anaesthetic, containing lidocaine (2.5 $mg\,ml^{-1}$) and epinephrine (5 $\mu g\,ml^{-1}$), was injected under the cervical mucosa and the uterus was removed through the vagina and the vaginal cuff was closed with a continuous suture.

The vaginal and laparoscopic hysterectomies group included both hysterectomies and hysterectomies with salpingo-oophorectomy.

In the postanaesthesia care unit (PACU), postoperative pain was treated with patient-controlled analgesia (PCA; Abbott Pain Management Provider; Abbott Laboratories, North Chicago, Illinois, USA, or CADD Legacy PCA; Smiths Medical MD, Inc., St. Paul, Minnesota, USA): with oxycodone 1 $mg\,ml^{-1}$solution, an oxycodone bolus dose of 2 mg and a lock-out interval of 10 min. If the

patient reported pain more than 3 on the NRS pain score, then rescue pain medication (i.v. bolus of oxycodone 3 mg) was given in the PACU. While on the ward, the PCA was continued for at least 20 h after surgery. Paracetamol 1 g was administered i.v. every 6 h. If nausea occurred, the patients were given either a bolus of i.v. ondansetron 4 mg or i.v. droperidol 0.75 mg. Data for the NRS pain scores at rest and with coughing, and the cumulative consumption of oxycodone were collected for 20 h by a nurse, at 0, 10, 20, 30 and 60 min, and then at 2, 4, 6 and 20 h, starting with a patient's arrival in the PACU.

A pain questionnaire with a prestamped return envelope was mailed to the patients 6 months after surgery. If this was not returned within 4 weeks, a reminder was sent. Patients were considered to have persistent posthysterectomy pain at this time if they reported either having had pain since surgery or currently had pelvic pain that had started sometime after surgery. Those patients who had persistent posthysterectomy pain were asked to answer questions concerning the frequency, location, character and intensity of the pain, whether the pain interfered with sleep or their daily activities, and how they managed the pain. All patients were asked about their working status and about pain problems other than pelvic pain. The English translation of the questionnaire is shown in Appendix 1, http://links.lww.com/EJA/A75.

Data regarding the patients' characteristics and surgical outcomes (age, smoking, type of surgery, main indication of surgery, uterine weight, estimated blood loss, remifentanil consumption, anaesthetic and perioperative complications) were collected from the patients' medical records (Table 1).

Statistical analysis

Results are shown as percentages or mean with SD. Chi-square or Fisher's exact test was employed to assess differences in categorical variables. A univariable logistic regression model was used to identify factors that were related to persistent posthysterectomy pain. Variables with a *P* value less than 0.20 in the univariable analysis were included in the final (forward stepwise) multivariable logistic regression analysis. Differences between groups were considered significant at *P* value less than 0.05.The statistical analysis was performed using SPSS, Windows version 19.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Of the original 267 patients, 25 were excluded because the surgery was converted to laparotomy, or the hysterectomy was not performed, or the inclusion criteria were otherwise not fulfilled. Thus, the questionnaire was sent to 242 patients and 227 responded (94%). Of these 227, 88 had undergone vaginal and 139 laparoscopic hysterectomy. The main indications were uterine leiomyoma (148), menstrual disorders (45), pelvic pain (9) and other (25). One patient who had reported persistent pelvic pain at 6 months did not answer the rest of the questions concerning pelvic pain, and 18 patients had not answered the question regarding preoperative pain. The patients' characteristics and surgical outcomes are presented in Table 1.

Table 1 Patients' characteristics and surgical outcomes ($n = 227$)

Age (years), mean (SD)	49 (7.2)
Working status, *n* (%)	
Working full-time	168 (74.0)
Working part-time	12 (5.3)
On a leave of absence	5 (2.2)
Unemployed or laid off	9 (4.0)
Sick leave	3 (1.3)
Retired or on a rehabilitation grant	20 (8.8)
Studying	3 (1.3)
Other	7 (3.1)
Smoking, *n* (%)	
Yes[a]	41 (18.1)
Type of hysterectomy, *n* (%)	
Laparoscopic	139 (61.2)
Vaginal	88 (38.8)
Uterus weight (mg), median (Q_1 to Q_3)	200 (135 to 319)
Estimated blood loss (ml), median (Q_1 to Q_3)	100 (50 to 200)
Remifentanil consumption (μg), mean (SD)	1109 (473)
Anaesthetic, *n* (%)	
Propofol	158 (69.6)
Sevoflurane	69 (30.4)
Complication, *n* (%)	
All together	42 (18.5)
Hematoma	19 (8.4)
Infection	16 (7.0)
Other[b]	7 (3.1)

Q_1, lower quartile; Q_3, upper quartile; SD, standard deviation. [a]Smoking status of one patient is missing. [b]Other complications were ureter injuries, urinary bladder injuries, occlusions of the intestine and vesicovaginal fistula.

Six months after surgery, 26% (59/227) of the patients had pelvic pain. Before surgery, 68.4% (143/209) of the women had no pain, while 31.6% (66/209) reported pelvic pain at rest, and 29.7% (62/209) pain on moving. Of the women who had no pain before surgery, 27 (18.9%) had persistent pain after surgery. One patient had pain that lasted more than 3 months after surgery but had no pain 6 months after surgery. Of the 225 patients with data, 58 (25.8%) reported that they had pain other than in the pelvic area: back, neck, hip, upper or lower extremities, head, upper abdomen. This pain was reported to be either in addition to the pelvic pain or it was the only pain. Twenty-six (44.8%) patients with persistent pelvic pain also reported pain elsewhere, mostly in the bones and joints (16/26).

Six months after hysterectomy, most of the patients still experiencing pain rated their average pain as mild (NRS 0 to 3) and four of the 58 (6.9%) patients rated their worst pain as severe (NRS 7 to 10) (Table 2). Pain occurred less than once a week in 43.1% of patients. When completing the questionnaire, six patients had no pain (NRS 0) during the previous week, although they reported having persistent pelvic pain. The location and character of the

Table 2 Pain scores 6 months after surgery ($n = 58$)

	NRS 0 to 3	NRS 4 to 6	NRS 7 to 10
Pain intensity			
Current pain	44 (75.9)	13 (22.4)	1 (1.7)
Average pain during the past week	38 (65.5)	18 (31.0)	2 (3.4)
The worst pain during the past week	30 (51.7)	24 (41.4)	4 (6.9)

Data are *n* (%). NRS, numeric rating scale.

pain varied between the patients (Table 3). Pain affected sleeping in 27.6% (16/58) of patients. Eighteen of the 58 (31.0%) patients used some analgesics: one used paracetamol-codeine and the others either anti-inflammatory analgesics or paracetamol. Ten (17.2%) had received other forms of treatment for their pain, mostly physiotherapy. For 21 patients (36.2%), the pain did not interfere with their daily activities (NRS 0), and for 27 (46.5%), it interfered a little with their daily activities (NRS 1 to 3). For 9 (15.5%) women, the pain had a moderate effect on their daily activities (NRS 4 to 6). One patient experienced significant restriction of her daily activities due to her pain (NRS 8).

Three factors were significantly associated with pain at 6 months in our multivariable logistic regression model (Table 4): smoking, acute postoperative pain on coughing 4 h after surgery and a laparoscopic procedure. The more severe the pain during the first 20 postoperative hours, the more likely the patient was to suffer from persistent pain 6 months after hysterectomy. The correlation was most significant for the 4-h time point and so this pain score was entered in the univariate analysis. The pain score at 1 h was also included in the analysis because this was the first time point when all the patients were alert enough to score their acute pain while coughing. Despite the correlation between persistent pain and severe early postoperative acute pain, the cumulative consumption of oxycodone in the acute phase was similar between patients who developed persistent pain and those who did not. The relationship between preoperative pain and persistent postoperative pain is complex. In the univariate analysis, the intensity of preoperative pain had a significant correlation with persistent pain; however, this was not so in in the multivariable model (Table 4). But patients who reported severe preoperative pain (NRS 7 to 10) benefited from surgery in terms of pain relief: six patients with severe pain on movement preoperatively had no persistent pelvic pain 6 months after hysterectomy; three further patients with severe preoperative pain reported persistent pelvic pain 6 months after surgery, but their average pain score during the week before the questionnaire was zero.

Table 3 Pain characteristics 6 months after surgery ($n = 58$)

	n	Percentage
Pelvic pain frequency		
Incessant, constant	2	3.4
Incessant, varying in strength	8	13.8
Daily bouts of pain	2	3.4
Frequent bouts of pain, but not every day	21	36.2
Occurs less than once a week	25	43.1
Location		
In the middle of the lower abdomen	23	39.7
In the vagina	6	10.5
In the groin	19	32.8
In the lower back	25	43.1
Around the operation scar	4	6.9
Elsewhere	9	17.0
Characteristic of pain		
Ache	17	29.3
Tenderness	24	41.4
Burning sensation	12	20.7
Other	21	36.2

There were more complications after laparoscopic hysterectomy (24.7%) than after vaginal hysterectomy (8.7%). Age, the choice of anaesthetic, the consumption of remifentanil during anaesthesia, the weight of uterus or estimated blood loss were not associated with persistent pain 6 months after hysterectomy.

Discussion

The results of this prospective study show that persistent postsurgical pain is a common problem after hysterectomy, but for most of the patients, the intensity of pain is mild and the pain is not continuous. In the multivariable logistic regression, smoking, the severity of acute postoperative pain after surgery and a laparoscopic surgical technique were all associated with persistent pain at 6 months after hysterectomy.

Persistent pain after surgery is a misery for any individual patient, and since the 1990s, several studies have reported considerable variations in the incidence of persistent postsurgical pain with different types of surgery.[11,12] Despite the many years of interest in the subject, the definition of persistent postoperative pain is not standardised,[13] hence, we would encourage the development of a widely acceptable definition on the basis of common criteria. Because persistent postoperative pain has the potential to restrict lifestyle, we chose to use a low threshold for our definition.

Most hysterectomies are performed for benign conditions and the surgery is expected to resolve the symptoms, leading to a better quality of life.[14] The prevalence of persistent pain after hysterectomy varies markedly in previous studies, ranging from 5 to 50%,[6,15] but the influence of other underlying causes of chronic pelvic pain in these studies is unclear.[3] In our study,

Table 4 Factors associated with persistent pain 6 months after hysterectomy

	Persistent pain		Univariate		Multivariable	
	n	Percentage	OR (95% CI)	*P*	OR (95% CI)	*P*
All patients ($n=227$)	59	26.0				
Pain at rest 1 h after surgery (NRS 0 to 10)			1.10 (0.96 to 1.27)	0.167		
NRS 0 to 3 ($n=69$)	15	21.7				
NRS 4 to 6 ($n=111$)	29	26.1				
NRS 7 to 10 ($n=47$)	15	31.9				
Pain on coughing 1h after surgery (NRS 0 to 10)			1.13 (0.99 to 1.30)	0.080		
NRS 0 to 3 ($n=50$)	7	14.0				
NRS 4 to 6 ($n=108$)	32	29.6				
NRS 7 to 10 ($n=67$)	19	28.4				
Pain at rest 4 h after surgery (NRS 0 to 10)			1.26 (1.07 to 1.49)	0.007		
NRS 0 to 3 ($n=160$)	34	21.3				
NRS 4 to 6 ($n=57$)	21	36.8				
NRS 7 to 10 ($n=6$)	3	50.0				
Pain on coughing 4h after surgery (NRS 0 to 10)			1.26 (1.08 to 1.47)	0.003	1.22 (1.02 to 1.44)	0.025
NRS 0 to 3 ($n=122$)	25	20.5				
NRS 4 to 6 ($n=81$)	23	28.4				
NRS 7 to 10 ($n=18$)	9	50.0				
Preoperative pain at rest (NRS 0 to 10)			1.28 (1.09 to 1.51)	0.004		
NRS 0 to 3 ($n=188$)	45	23.9				
NRS 4 to 6 ($n=17$)	7	41.2				
NRS 7 to 10 ($n=4$)	2	50.0				
Preoperative pain on moving (NRS 0 to 10)			1.20 (1.05 to 1.38)	0.010		
NRS 0 to 3 ($n=180$)	42	23.3				
NRS 4 to 6 ($n=21$)	9	42.9				
NRS 7 to 10 ($n=8$)	3	37.5				
Smoking						
Yes ($n=41$)	19	46.3	3.23 (1.59 to 6.57)	0.001	3.80 (1.67 to 8.67)	0.001
No ($n=185$)	39	21.1	Reference			
Type of surgery						
Laparoscopic ($n=139$)	43	30.9	2.02 (1.05 to 3.87)	0.035	2.43 (1.12 to 5.24)	0.024
Vaginal ($n=88$)	16	18.2	Reference			
Complication						
None ($n=185$)	45	24.3	Reference			
All together ($n=42$)	14	33.3	1.56 (0.75 to 3.21)	0.232		
Haematoma ($n=19$)	5	26.3				
Infection ($n=16$)	5	31.3				
Other ($n=7$)	4	57.1				
Anaesthetic						
Propofol ($n=158$)	41	25.9	1.00 (0.52 to 1.89)	0.983		
Sevoflurane ($n=69$)	18	26.1	Reference			
	Mean	SD				
Age (years)	48.9	7.3	0.99 (0.95 to 1.03)	0.504		
Remifentanil consumption (10 μg)	119.1	48.8	1.01 (1.00 to 1.01)	0.125		

NRS, numeric rating scale.

the prevalence of persistent pain 6 months after hysterectomy was 26% but, if patients were pain free before surgery, this reduced to 18.9%. An earlier prospective study reported a 17% prevalence of persistent pain 4 months after hysterectomy: 63% (57/90) abdominal hysterectomy, 28% (25/90) vaginal hysterectomy and 9% (8/90) laparoscopically assisted vaginal hysterectomy.[4] In that study, pain was considered to be clinically relevant pain only if it interfered with daily living, whereas, in our current study, any persistent pelvic pain 6 months after surgery was included in the prevalence. Another prospective study found a 50% prevalence of posthysterectomy pain 4 months after surgery when all pain linked to the surgical procedure was included.[6] A prospective study of elective gynaecologic surgery reported a 14% incidence of chronic postsurgical pain 6 months after surgery.[5] In these studies, the most common procedure was abdominal hysterectomy (70%).[5,6] A minimally invasive surgical technique is expected to decrease the incidence of persistent pain[1]; thus, it was unanticipated that we would observe persistent posthysterectomy pain to be so common after vaginal and laparoscopic surgery. However, it should be noted that, in our study, for most patients still experiencing pain at 6 months, the pain was mild (NRS 0 to 3), and only four of the 58 patients (6.9%) had severe pain (NRS 7 to 10 at its worst during the previous week). Nearly half of the patients suffered only from occasional pain (less than once a week), and for 21 out of 58 (36.2%) patients, the pain did not interfere with their daily activities. Because there was no validated questionnaire for persistent posthysterectomy pain, our questionnaire was modified

from one used widely in Finnish pain clinics. The patients were asked to describe their pain as ache, tenderness, burning sensation or in their own words, but, in order to assess the type of pain more accurately, more specific questions about the character of the pain should have been asked.

As in earlier investigations,[16–18] our study showed a correlation between the intensity of early postoperative acute pain and persistent postsurgical pain. A possible reason for this apparent association could be due to variations in an individual's pain sensitivity. Although genetic traits[19] have been shown to explain some variation in pain sensitivity, there are also other factors, especially psychosocial factors, which have been linked to increased pain sensitivity.[17] In a recently reported study of 1000 women treated for breast cancer, anxiety was the most significant cofactor associated with increased pain sensitivity.[20] In the current study, the level of anxiety or other psychological factors was not recorded.

We found that the most significant correlation was that between smoking and persistent pain. Several epidemiological and prospective cohort studies have shown a correlation between smoking and chronic pain,[21,22] but there are also studies with conflicting results.[21,23] Although most studies have focused on back pain, a systematic review by Latthe *et al.*[3] found smoking to be one factor predisposing women to chronic pelvic pain. There are few studies that have investigated postoperative pain and smoking. Nicotine is known to have analgesic properties,[21,24] but its impact on postoperative acute pain is unclear. It is also uncertain whether the development of persistent pain in association with smoking is due to the smoking *per se*, or whether it is a consequence of some underlying condition that predisposes one to smoke, for example depression.[21,25] In contrast to our result, a recent large-scale prospective study of breast cancer patients found no association between persistent postsurgical pain and smoking.[26]

Previously, complications related to surgery have been linked to an increased risk of persistent postsurgical pain.[27] In our current study, although there was a trend towards a link between such surgical complications and persistent postsurgical pain, this did not achieve statistical significance and so we cannot definitively assign blame for the higher prevalence of pain in the laparoscopy group on the higher rate of complications. Neither the choice of anaesthetic, propofol or sevoflurane, nor the consumption of remifentanil had any correlation with persistent pain. Thus, our results do not support the findings of a previous retrospective study investigating chronic pain after breast cancer surgery, which found that patients anaesthetised with propofol had a lower incidence of chronic pain than those patients anaesthetised with sevoflurane.[28]

A strength of the current study is that not only was it was prospective, with a standard protocol for anaesthesia, postoperative medication and data collection, but also there was a high percentage of patients who returned their questionnaires. However, the patients are not representative of the whole population of women who undergo hysterectomy. This was a follow-up study of two earlier studies concerning acute postoperative pain and includes only laparoscopic and vaginal hysterectomies, without randomisation. Furthermore, obese and diabetic patients were excluded, as were patients with chronic preoperative pain who required opioids for that pain. A correlation between anxiety and/or depression and persistent postoperative pain has been shown, most recently by Pinto *et al.*,[6] but because we did not collect data on depression and/or anxiety, we are unable to comment on this.

In conclusion, after laparoscopic or vaginal hysterectomy, persistent postsurgical pain is common but, for most of the women, the intensity of the pain is mild and there is minimal interference with daily activities. The most significant risk factors for persistent postsurgical pain were smoking, severe early postoperative pain and a laparoscopic procedure.

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Clinical pain research

Characterization of persistent pain after hysterectomy based on gynaecological and sensory examination

Satu M. Pokkinen[a,*], Kari Nieminen[b], Arvi Yli-Hankala[a,c], Maija-Liisa Kalliomäki[a]

[a] Department of Anaesthesia, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland
[b] Department of Obstetrics and Gynaecology, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland
[c] University of Tampere, School of Medicine, FI-33014 University of Tampere, Finland

HIGHLIGHTS

- Persistent pelvic pain after hysterectomy can be defined as persistent postsurgical pain - PPSP - in most cases.
- The nature of PPSP is probable neuropathic on more than half of these patients.
- Pain has an impact on the patients' health related quality of life.

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ABSTRACT

Background and aims: Previous studies have shown that pelvic pain is common after hysterectomy. It is stated that only a minor part of that pain can be defined as persistent postsurgical pain. Our primary aim was to find out if the pelvic pain after hysterectomy may be classified as postsurgical. Secondary aims were to characterize the nature of the pain and its consequences on the health related quality of life.
Methods: We contacted the 56 women, who had reported having persistent pelvic pain six months after hysterectomy in a previously sent questionnaire. Sixteen women participated. Clinical examinations included gynaecological examination and clinical sensory testing. Patients also filled in quality of life (SF-36) and pain questionnaires.
Results: Ten out of sixteen patients still had pain at the time of examination. In nine patients, pain was regarded as persistent postsurgical pain and assessed probable neuropathic for five patients. There were declines in all scales of the SF-36 compared with the Finnish female population cohort.
Conclusions: In this study persistent pelvic pain after vaginal or laparoscopic hysterectomy could be defined as persistent postsurgical pain in most cases and it was neuropathic in five out of nine patients. Pain had consequences on the health related quality of life.
Implications: Because persistent postsurgical pain seems to be the main cause of pelvic pain after hysterectomy, the decision of surgery has to be considered carefully. The management of posthysterectomy pain should be based on the nature of pain and the possibility of neuropathic pain should be taken into account at an early postoperative stage.

1. Introduction

The prevalence of chronic pelvic pain is estimated to be 3.8% in primary health care female patients [1]. Hysterectomy is one of the most frequent surgical operations on women for benign causes [2] and previous studies have shown that persistent pain is common after hysterectomy. However, the prevalence varies significantly in these studies, ranging from 5% to 50% [3–8]. Persistent postsurgical pain (PPSP) is pain that is not a continuum of preoperative pain, continues for longer than two months and cannot be explained by any other aetiology except surgery [9]. Pain is one of the symptoms leading to the decision of hysterectomy. Due to the differences in pain assessment and lack of clinical examinations in previous studies it remains unclear how big a proportion of the pelvic pain can be defined as PPSP [5,6,10]. The aetiology of PPSP has traditionally been considered neuropathic [11,12]. However, it is known that nerve damage is not essential. Peripheral inflammation can affect the central nervous system and contribute to persistent pain

* Corresponding author. Tel.: +358 3311611; fax: +358 331164363.
E-mail address: Pokkinen.Satu.M.@student.uta.fi (S.M. Pokkinen).

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[13]. It is also shown that postsurgical neuropathies can be solely inflammatory and there is no need for mechanical trauma [14].

There are clear inconsistencies in the definition of neuropathic pain, which makes the classification of pain difficult [15]. According the International Association for the Study of Pain (IASP) neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [16]. A clinical examination is the only way to reliably assess the nature of persistent postsurgical pain and to exclude other causes of pain.

Health related quality of life (HRQoL) has recently been on the focus in comparing different methods of hysterectomy. The method of surgery does not have an impact on the HRQoL [17,18]. Lang et al. have studied the HRQoL in middle-aged women and found that the more conditions the women have, the lower the HRQoL is, with each condition lowering the score [19].

We designed a prospective, observational study with clinical analysis of pain. Our primary aim was to find out the proportion of PPSP in women who suffer from persistent pelvic pain after laparoscopic or vaginal hysterectomy. Our secondary aims were to clarify the characteristics of pain and to assess patients' HRQoL.

2. Methods

The study was carried out during the period of May 2012 and November 2013. An invitation letter was sent to patients ($n = 56$) who previously had reported presence of persistent pelvic pain six months after surgery. All 56 patients had participated to the follow-up study of persistent pelvic pain after vaginal or laparoscopic hysterectomy aiming to find out prevalence and predictors of persistent pain [7]. In that study the prevalence of persistent pelvic was 26%. Patients willing to participate in the study were asked to book an appointment. Written informed consent was obtained from 16 Finnish speaking women, who had undergone laparoscopic or vaginal hysterectomy with or without salpingo-oophorectomy for non-malignant conditions at Tampere University Hospital or Valkeakoski Regional Hospital carried out between October 2008 and March 2013 (Fig. 1). The study design was approved by the local Ethics Committee, Pirkanmaa Hospital District, Tampere, Finland, number R11190, approval date 21 February 2012 and registered with Clinical Trials (NCT01706549).

2.1. Examination

Clinical examinations included gynaecological examination by a gynaecologist (author K.N) and clinical sensory testing by an anaesthesiologist specialized in pain medicine (author M-L.K) and were performed in a lithotomy position. The examinations were performed during the same appointment and in the same order.

Gynaecological examination: Vulvar area was inspected and palpated. Vagina was examined first with a Sim's speculum and palpation in rest and then inspected and palpated during Valsalva manoeuvre. Pelvic area was palpated bimanually to detect scarring and mobility of the vaginal vault, adhesions or painful areas. All patients underwent transvaginal ultrasound.

Sensory examination: Patients were asked to keep eyes closed or look at the ceiling, following their preference. The examination started with Abeta-fibre sensory testing with a cotton stick. A light touch with the cotton stick was applied to the skin from above the umbilicus towards the groin, starting laterally and proceeding medially with 3 cm light swipes sequentially. In the thigh region similar sequential swipes were performed from upper lateral to lower medial part of the thigh. Then the examination proceeded to the vulvar and perineal region. In a similar manner, C-fibres and Adelta fibres were tested with warm (±40 °C) and cold (±25 °C) metallic strollers, rolling with the force of the weight of the stroller,

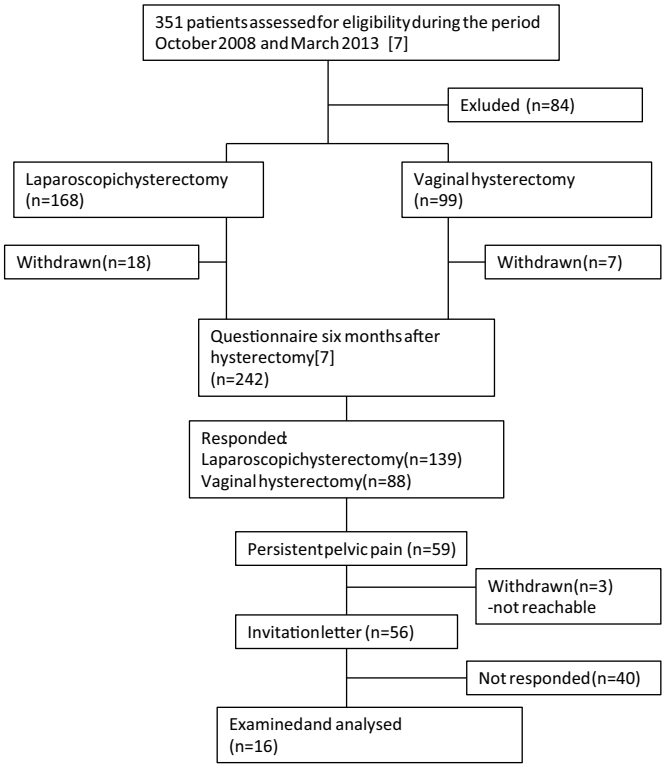

Fig. 1. Flowchart of the patients.

slowly on the skin (Somedic, Hörnby, Sweden) and cocktail sticks (pin prick) with 2–3 cm intervals with the forefinger of the examiner on the other end of the cocktail stick in order to have some control on the force of the pressure applied. The patients were asked to compare sides, or when both altered, to another nearby skin area, and rate the change on the numerical rating scale (NRS) (0–10). Presence of allodynia and/or temporal and/or spatial summation was asked verbally. The results were drawn and written on a separate chart.

2.2. Questionnaires

The participants filled in the pain and SF-36 questionnaires after the appointment and they were asked to drop the filled questionnaire into an indicated box before leaving the hospital. The pain questionnaire was the same, which they had completed also at time point six months after hysterectomy [7]. Patients were asked if they still had persistent pelvic pain. Those patients who had persistent pelvic pain were asked to answer the questions concerning frequency, location, character and intensity of pain, the interference of pain with sleeping and daily activities, and management of pain. All patients were asked about other pain problems than pelvic pain and their working status. They were also asked to fill in SF-36 which is a 36-item generic health status measure [20]. The SF-36 assesses eight scales concerning physical functioning, role physical, role emotional, vitality, mental health, social functioning, bodily pain and general health.

2.3. Neuropathic pain probability

Because neuropathic pain is not a single disease but a syndrome with specific symptoms and signs, the probability of neuropathic pain is assessed by a neurological history and an examination. The examination includes sensory testing, definition of neural area as in Apte et al. [21]. In this study we used a grading system

Table 1
Patients characteristics and pain data.

Number	Age (years)	Time to examination (months)	Type of surgery	Indication of surgery	Complication	Smoking	Preoperative pain R/M (NRS)	Pain at the appointment	PPSP
1	47	12	LH + SO	Menstrual disorders	No	No	8/8	Yes	No
2	45	32	VH	Uterine leiomyoma	No	Yes	2/0	Yes	Yes
3	55	32	VH	Cervical dysplasia	No	Yes	0/0	Yes	Yes
4	56	33	VH	Uterine leiomyoma	No	No	N/A	No	No
5	55	25	LH + SO	Uterine leiomyoma	Ureter injury	No	0/0	Yes	Yes
6	50	10	LH + SO	Uterine leiomyoma	No	No	0/0	Yes	Yes
7	49	11	LH + SO	Uterine leiomyoma	Urinary bladder injury	Yes	4/6	Yes	Yes
8	50	22	LH + SO	Cervical dysplasia	No	No	0/0	No	No
9	47	30	LH	Uterine leiomyoma	No	No	3/8	No	No
10	48	23	LH	Menstrual disorders	No	Yes	6/6	No	No
11	57	26	LH	Cervical dysplasia	No	Yes	0/0	Yes	Yes
12	58	30	LH + SO	Uterine leiomyoma	No	No	2/2	Yes	Yes
13	69	35	LH	Endometrial hyperplasia	Hematoma, infection	No	0/0	No	No
14	41	39	LH	Endometrial hyperplasia	No	No	0/0	No	No
15	51	39	LH + SO	Uterine leiomyoma	No	Yes	N/A	Yes	Yes
16	47	44	LH	Uterine leiomyoma	No	No	N/A	Yes	Yes

VH, vaginal hysterectomy; LH, laparoscopic hysterectomy; SO, salpingo-oophorectomy; R/M, at rest/on moving; NRS, numerical rating scale 0–10; PPSP, persistent postsurgical pain; N/A, not available.

published previously by European Federation of Neurological Societies [15,22]. This grading system is based on the history of pain, the clinical sensory examination (touch/vibration, cold, warmth and pain sensibility) and the diagnostic tests e.g. skin biopsy. In the current study pain was classified as possible neuropathic pain, if pain was located in the surgical or corresponding area and character of pain fulfilled neuropathic criteria (history of pain). Pain was classified as probable neuropathic pain if the clinical sensory testing showed the presence of sensory disturbances in addition to the positive history of pain. Because we used no specific diagnostic test, no definite neuropathic pain was categorized.

2.4. Statistics

Results are shown as median or mean with SD. The statistical analysis was performed using SPSS™, Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Sixteen women participated in the study and underwent both gynaecological and sensory examination. The participation rate was 29%. The time from surgery to examination ranged from 10 to 44 months (median 30). The mean age was 51 (SD 6.6), range 41–69 years. Characteristics of patients are shown in Table 1.

3.1. Pain

Ten patients out of sixteen still had persistent pelvic pain. One of those ten patients had pain in the vagina only occasionally. This was regarded as pelvic pain but not PPSP. Pain for nine out of ten patients was regarded as PPSP, hence we did not find any other reason for persistent pelvic pain than the postoperative state. The only findings of gynaecological examination were an atrophic, dry vagina in two patients but that was not regarded as a cause of pelvic pain. Eight out of sixteen patients had sensory signs, and two of them without persistent pelvic pain. The sensory dysfunction was most often hyperesthesia located in the sensory area of iliohypogastric nerve (five out of eight) but also in the sensory area of genitofemoral (four out of eight), ilioinguinal (three out of eight), genital branch and scar. Fig. 2 illustrates the findings of the sensory examination and the results are specified according to affected nerve and NRS rating of the sensory dysfunction in Table 3.

Fifteen patients filled in the pain questionnaire. One out of these fifteen did not fill in the questionnaire properly and the rating of the intensity of pain was lacking. One patient did not fill in the pain questionnaire although she reported persistent pelvic pain in the clinical examination. According to the questionnaires the intensity of pain was mild for one patient, moderate for five patients and severe for one patient during the past week before the clinical examination. One patient reported that her pain occurs less than once a week and had no pain during the past week. Six patients had no more pain.

According to the pain questionnaire and the clinical examination we considered that nine patients had PPSP and determined the neuropathic pain as possible for three patients, probable for five patients and unlikely for one patient. The characteristics of pain are shown in Table 2 and the findings of sensory testing in Fig. 2 and Table 3.

3.2. Health related quality of life

All sixteen patients filled in the SF-36. The mean scores of the patients involved in this study were compared with the mean

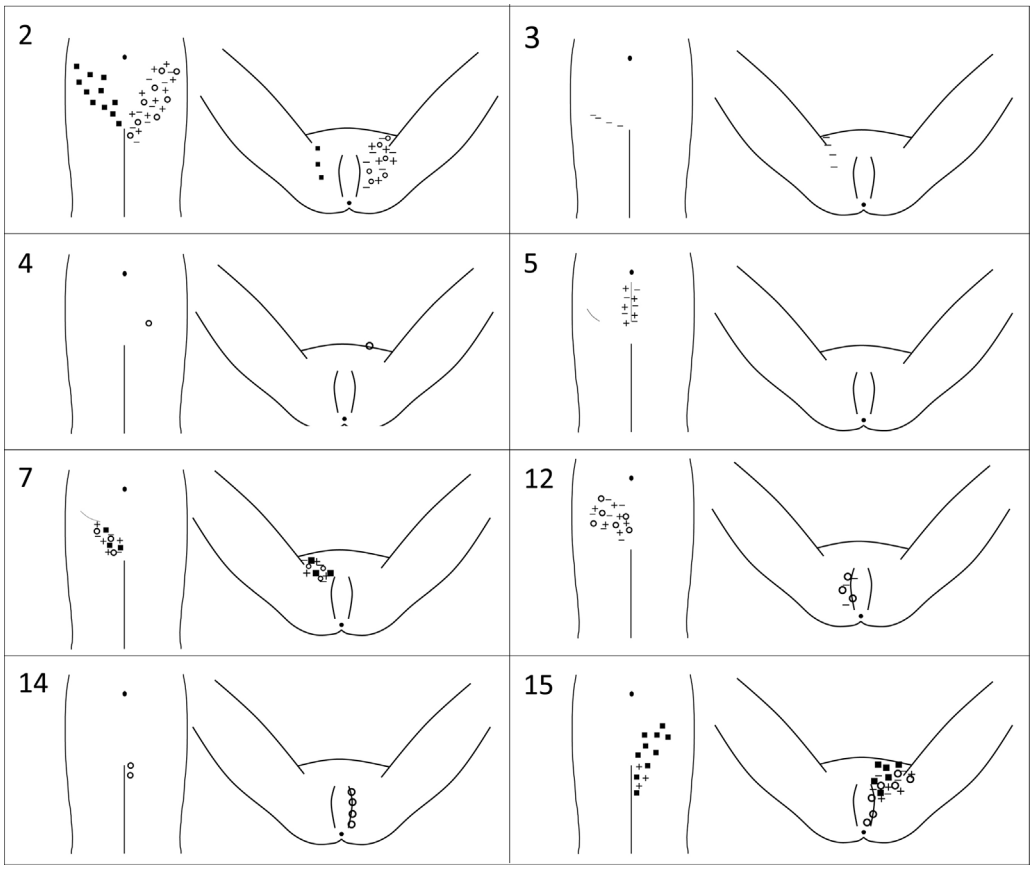

Fig. 2. Drawings showing the sensory changes in eight patients. + corresponds for warm, − for cold, both examined with the thermal roller. Black square ■ stands for touch (cotton stick) and open circle ○ for pin prick (wooden stick). The numbers in the left corner correspond to the patient id of this study.

Table 2
Characteristics of persistent pelvic pain.

Patient number	Location of pain	Description	When	Current pain (NRS)	Pain during the past week (NRS)	Pain at its worst during the past week (NRS)	Interfere with sleep	Interfere with daily activities (NRS)	Neuropathic pain
1 ≠	In the vagina	Ache, burning sensation	Occurs less than once a week	2	7	7	No	5	Possible
2	In the middle of the lower abdomen	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Probable
3	In the middle of the lower abdomen	Burning sensation	Occurs less than once a week	0	5	5	No	0	Probable
5	Pain when urinating	Tenderness	Daily bouts of pain	4	4	6	No	1	Possible
6	On the right side of the lower abdomen	Tenderness	Occurs less than once a week	5	5	5	No	2	Possible
7	In the middle of the lower abdomen	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Probable
11	In the middle of the lower abdomen	Ache	Occurs less than once a week	0	0	0	No	0	Unlikely
12	In the groin, in the lower back, on the right side of the lower abdomen	Tenderness, dull	Incessant, constant	4	4	5	No	4	Probable
15*	In the lower back, around the scar, on the right side of the lower abdomen	Ache, twinge	Daily bouts of pain	5*	5*	7*	Yes*	8*	Probable
16	On the right side of the lower abdomen	Tenderness	Weekly bouts of pain, but not daily	2	2	1	Yes	0	Possible

NRS (numerical rating scale 0–10), ≠ Patient number 1: no PPSP, *Patient number 15: back pain the worst pain.

Table 3
Sensory findings by anatomical distribution [21] and magnitude of sensory dysfunction by modulation on a NRS. + for hyperesthesia and − for hypoesthesia.

Patient id	Area or nerve(s)	Warm	Cold	Touch	Pin prick	Notes
2	Ilioinguinal	+4 l.sin	+4 l.sin	+5 l.dx	+3 l.sin	
	Iliohypogastric	+4 l.sin	+4 l.sin	+5 l.dx	+3 l.sin	
	Genitofemoral	+4 l.sin	+4 l.sin	–	+3 l.sin	
3	Ilioinguinal	–	−8 l.dx	–	–	
4	Iliohypogastric	–	–	–	+3 l.sin	AllodyniaTemporal and spatial summation
5	Scar		−5 l.a	–	+5	
7	Iliohypogastric	+3 l.dx	+3 l.dx	+3 l.dx	+3 l.dx	Temporal summation
12	Iliohypogastric	−2 l.dx	+7 l.dx	–	+3 l.dx	
	GenitofemoralGenital branch	–	+5 l.dx	–	+1 l.dx	
14	GenitofemoralGenital branch	–	–	–	+8 l.sin	Allodynia
15	Ilioinguinal	−8 l.sin	+8 l.sin	−8 l.sin	+8 l.sin	
	Iliohypogastric	–	–	+3 l.sin	–	
	Genitofemoral	-	+6 l.sin	+3 l.sin	+6 l.sin	

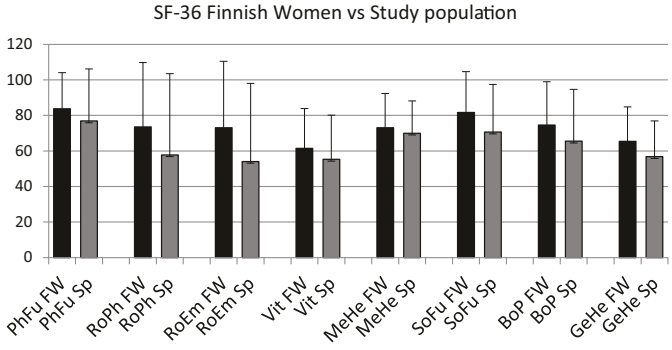

Fig. 3. Histogram showing quality of life in Study population (Sp) in comparison to Finnish Women (FW). PhFu = Physical Functioning, RoPh = Role Physical, RoEm = Role Emotional, Vit = Vitality, MeHe = Mental Health, SoFu = Social Functioning, BoP = Bodily Pain, and GeHe = General Health.

scores of Finnish female cohort ($n = 1133$) [23]. There were lower scores in all scales. Because of the small number of study patients, we did not regard a statistical analysis relevant (Fig. 3).

4. Discussion

The results of this descriptive study showed that the major part of chronic pelvic pain after vaginal or laparoscopic hysterectomy can be regarded as persistent postsurgical pain. Yet, the characteristics of PPSP varied. Our study also indicated that the persistent pelvic pain has an impact on patients' HRQoL.

It has been suggested that the surgery itself would have only minor impact on the persistent pelvic pain after hysterectomy. A study of ninety women who underwent hysterectomy reported that out of the fifteen patients who suffered from persistent pelvic pain four months after surgery, only four had PPSP. Persistent postsurgical pain was defined as a pain that affected daily living and was classified as newly acquired pain [10]. The study of persistent pain after elective gynaecologic surgery of 433 women found 14% incidence of PPSP. In that study PPSP was defined as a pain that the patient believed to be related to the previous surgery. The overall prevalence of pain was 35% six months after surgery [6]. The recent prospective multicentre study of different kind of surgeries reported 11.8% incidence of PPSP after vaginal and 25.1% after abdominal hysterectomy. The definition of PPSP based on Brief Pain Inventory and clinical sensory testing four months after surgery [8]. In our cohort nine out of ten women with pain were assessed to have PPSP despite that three of them had reported preoperative pelvic pain. Their preoperative pain was linked with menstrual bleeding and uterine leiomyomas and the persistent pain after surgery was not regarded as a continuum of this preoperative pain. The method of determining the PPSP after hysterectomy may account for the discrepancy between results. Our study confirms the significance of the clinical analysis of pain.

In the current study, the prevalence of probable neuropathic pain was five out of nine patients (56%) among patients with PPSP assessed according to the European Federation of Neurological Societies (EFNS) guidelines. This is within the limits of the results of a multicentre questionnaire survey with a six months prospective follow-up using the Douleur Neuropathique 4 Questions (DN4) [24]. According to that study 43.3% of the patients who reported PSPP had neuropathic pain, although the percentage ranged widely after various types of surgery. Among the patients who had undergone laparoscopic inguinal hernia repair the estimate for a neuropathic PSPP was 6%, open inguinal hernia repair 43% and caesarean section 61%. In a recently published systematic literature review the results were similar. The assessed prevalence of neuropathic pain among patients with PPSP was 52–66% after thoracic surgery, 68–74% after breast surgery, 31–45% after hernia surgery and 6–9% after total hip and knee arthroplasty [15]. The large multicentre study including vaginal and abdominal hysterectomies found that only 24% of patients with PPSP had neuropathic pain after vaginal hysterectomy and 44% after abdominal hysterectomy assessed by DN4 [8]. In our study two women of nine PPSP patients had undergone vaginal hysterectomy while in seven cases laparoscopic hysterectomies were performed. Sensory changes were seen equally after vaginal or laparoscopic hysterectomy. It is proposed that different combinations of mechanisms may cause the persistent pain after laparoscopic groin hernia repair [25]. Although patients frequently have sensory disturbances after inguinal herniotomy [26,27] these are not necessarily due to intraoperative nerve damage. Central sensitization due to peripheral inflammation may also account for the sensory dysfunction [15,28]. It is conceivable that this kind of mixed pathogenic mechanism is also involved in the development of persistent pain after hysterectomy.

It is known from earlier studies that the persistent postsurgical pain attenuates in time [24,29,30]. In our study, six patients out of sixteen were painless although they had reported having pain six months after hysterectomy. The time from surgery to examination ranged from 12 to 39 months (median 26.5) for these six patients.

Two patients with persistent pain had surgical complications, one ureter injury and one urinary bladder injury. These severe complications are rare, incidence 0.3–1.2% after laparoscopic hysterectomy [31,32]. For these two patients the complication may explain persistent pain. Another patient had severe pelvic pain and

this pain was not regarded as PPSP; i.e. ache and burning sensation in the vagina. The cohort study of 2397 patients by Dualé et al. found that intensity of pain was severe if the pain was neuropathic [24]. We did not find any association between probability of neuropathic pain and severity of pain but this can be explained by a small sample size. One patient who rated her pain moderate informed that her worst pain problem was back pain. It is shown earlier that comorbid chronic pain is associated with the intensity of PPSP [33]. Our results of SF-36 are consistent with the previous studies of PPSP and quality of life [34,35]. We found lower scores in all assessed scales compared with the Finnish female cohort although not all of the women examined had pelvic pain anymore. However, all sixteen women had reported to suffer persistent pelvic pain six months after hysterectomy.

The main limitation of the study is the low participation rate. The reason for the unwillingness to be involved in the study remains unknown. One explanation can be that the patients' persistent pain had disappeared and they thus found an option for another medical examination unnecessary. Attenuation of PPSP has been shown in a cohort of inguinal hernia patients [36]. The second limitation is that two of ten patients who suffered persistent pelvic pain did not fill in the pain questionnaire and these patients' data of the characteristic of pain were collected only from clinical examination records. Third, the time for clinical examination ranged being 10–44 months after surgery. The same time frame would have given us more reliable data to compare patients. It would be of relevance to plan a prospective study of persistent postsurgical pain with an objective on the time course of such a pain. Furthermore we did not ask the patients to fill in the SF-36 questionnaire preoperatively; therefore we were unable to compare the pre- and postoperative scores of SF-36 which would have been more informative. It is also noteworthy that clinical examination always has limitations in terms of the estimation of the origin of pain; e.g. is it whether musculoskeletal or gynaecological. Using a Vaginal Pressure-Pain Threshold-measurement by a specifically designed device [37] might have brought some additional value to our sensory testing. However, we did not regard this as a necessary part of this rather a pragmatic approach. The vaginal algometer has thus far been used in only one study [4], where researchers could in fact show a moderate correlation of persistent postoperative pelvic pain and pressure detection threshold. Further studies with such a device are warranted before it will be included as a part of clinical gynaecological examination. All and all, the sensory examination used in this study relies on subjective measures, as the measure of pain is always subjective and may be influenced by the state of mind, environment, and interaction between the examiner and the subject. In our study, the clinical gynaecological examination and the sensory testing were always performed by the same authors (KN and MLK, respectively), which is a strength and during the same session, when both of the examiners were present. We thus sought to alleviate the possible unintentional negative chemistry occurring between only two individuals.

5. Conclusions

In this study persistent pelvic pain after vaginal or laparoscopic hysterectomy could be defined as PPSP in most cases. The nature of persistent post-hysterectomy pain followed the characteristics of other types of PPSP being probable neuropathic for five out of nine patients. Pain had an impact on the patients' health related quality of life.

Conflicts of interest

None declared.

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