(Acta Anaesth. Belg., 2020, 71, 45-56)

Pain management after open inguinal hernia repair : an updated systematic review and procedure-specific postoperative pain management (PROSPECT/ESRA) recommendations

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Abstract : *Background* : Open inguinal hernia repair can be associated with moderate-to-severe postoperative pain, which can delay return to activities of daily living. The aim of this systematic review was to update the available literature and develop recommendations for optimal pain management after open inguinal hernia repair. A systematic review utilizing PROcedure SPECific Postoperative Pain ManagemenT (PROSPECT) methodology was undertaken.

Methods : Randomised controlled trials published in the English language between January 1st 2009 and August 31st 2019, evaluating the effects of analgesic, anesthetic, and surgical interventions were retrieved from MEDLINE, EMBASE and Cochrane Databases. Of 203 eligible studies identified, 37 studies met the inclusion criteria.

Results : Interventions that improved postoperative pain relief included paracetamol and nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 selective inhibitors, as well as local anesthetic infiltration and regional analgesia techniques such as ilio-hypogastric/ilio-inguinal nerve blocks and transversus abdominis plane blocks. Although effective, epidural analgesia or paravertebral blocks are considered invasive and harmful, and thus not recommended. Insufficient evidence was found for psoas block, extended release local anesthetics, wound infiltration using non-steroidal anti-inflammatory drugs, clonidine or opioids, topical conventional non-steroidal anti-inflammatory drugs, systemic clonidine, corticosteroids and ketamine, intravenous lidocaine infusion, cryoanalgesia techniques, and nerve section. Inconsistent evidence was found for the use of gabapentinoids.

Conclusion : The analgesic regimen for open inguinal hernia repair should include paracetamol and nonsteroidal anti-inflammatory drug or cyclooxygenase-2 selective inhibitor administered pre-operatively or intra-operatively and continued post-operatively. In addition, local anesthetic infiltration and/or a regional analgesia technique (ilio-inguinal nerve blocks or transversus abdominis plane blocks), with opioids used as rescue analgesics. Further studies are required to assess the role of novel regional analgesic techniques such as erector spinae blocks and to confirm the influence of the recommended analgesic regimen on postoperative pain relief in an enhanced recovery setting.

Key words : Open inguinal hernia repair ; pain ; analgesia ; systematic review ; evidence-based medicine.

Recommendations

1. Systemic analgesia should include paracetamol and a non-steroidal anti-inflammatory drug or cyclo-oxygenase-2 selective inhibitor administered pre-operatively or intra-operatively and continued post-operatively.
2. Local anesthetic infiltration and/or regional analgesia technique (ilio-hypogastric/ilio-inguinal nerve blocks or

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Paper submitted on May 25, 2020 and accepted on May 26, 2020.

Conflict of interest : PROSPECT is supported by an unrestricted grant from the European Society of Regional Anesthesia and Pain Therapy (ESRA). In the past, PROSPECT has received unrestricted grants from Pfizer Inc. New York, NY, USA and Grunenthal, Aachen, Germany. GPJ has received honoraria from Baxter and Pacira Pharmaceuticals. MVdV has received honoraria from Sintetica, Grunenthal, Vifor Pharma, MSD, Nordic Pharma, Janssen Pharmaceuticals, Heron Therapeutics and Aquettant. EP-Z has received honoraria from Mundipharma, Grunenthal, MSD, Janssen-Cilag GmbH, Fresenius Kabi and AcelRx.

transversus abdominis plane blocks) is recommended.
3. A single dose of intravenous dexamethasone is recommended for its ability to increase the analgesic duration of the block, decrease analgesic use, and antiemetic effects.
4. Opioids should be reserved as rescue analgesics in the post-operative period.

Why was this guideline developed?

Open inguinal hernia repair is associated with moderate-to-severe postoperative pain which may influence recovery. The aim of this guideline is to provide clinicians with an updated evidence for optimal pain management after open inguinal hernia repair.

What other guidelines are available on this topic?

The PROSPECT recommendations for pain management after open inguinal hernia repair have been published previously, however, an update assessing analgesic interventions was necessary.

How does this guideline differ from other guidelines?

The updated systematic review further confirms the previous recommendations. Also, an updated PROSPECT approach was used to develop the current recommendations such that the available evidence is critically assessed for current clinical relevance and the use of simple, non-opioid analgesic such as paracetamol and non-steroidal anti-inflammatory drugs as baseline analgesics. This approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, as well as balancing efficacy and adverse effects.

Introduction

Open Inguinal Hernia Repair (IHR) is associated with moderate-to-severe postoperative pain, which may delay recovery and return to activities of daily living (1). In addition, inadequate pain control can increase unplanned admission rate and readmission after discharge home (1). Furthermore, inadequate post-operative pain relief may lead to hyperalgesia and persistent postoperative pain (2).

Based on a systematic review performed in 2009, the PROSPECT (PROcedure SPECific Postoperative Pain ManagemenT) Working Group (3,4), which is a collaboration of surgeons and anesthetists, previously provided recommendations for pain management in patients undergoing IHR (5). A recent International guideline for groin hernia surgery provided non-specific statements regarding pain management recommending perioperative field blocks and/or subfascial/subcutaneous infiltrations and use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase (COX)-2 selective inhibitors (1). Therefore, an updated systematic review on analgesic interventions for pain management in IHR was performed. In addition, it was deemed necessary to reassess the recommendations to align them with the updated PROSPECT approach that considers current clinical relevance and clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, as well as balancing efficacy and adverse effects (6,7).

The aim of this update was to systematically review the available literature assessing the analgesic, anesthetic, and surgical interventions on pain after open IHR. Postoperative pain scores were the primary outcome measures. Other recovery outcomes assessed included cumulative opioid requirements and adverse effects, when reported, and the limitations of the data were reviewed. The ultimate aim was to develop recommendations for pain management after IHR.

Methodology

The methods of this review adhered to the PROSPECT methodology as previously reported (7). Specific to this study, the EMBASE, MEDLINE, PubMed and Cochrane Databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts or Reviews of Effects, Cochrane Database of Systematic Reviews) were searched for randomized controlled trials (RCTs) published between January 1st 2009 and August 31st 2019. The search terms used was (hernia OR inguinal OR inguinal hernia repair OR herniorrhaphy OR herniorraphy) AND (pain OR postoperative pain OR analgesia OR anesthesia OR anesthetic) AND (anesthetics neuraxial OR intrathecal OR spinal OR epidural analgesia OR paravertebral blocks OR peripheral nerve OR peripheral block OR regional nerve OR transversus abdominis plane block OR infiltration OR instillation OR NSAID OR COX-2 OR paracetamol OR acetaminophen OR gabapentin OR pregabalin OR clonidine OR opioid OR ketamine OR corticosteroid OR dexamethasone OR heavyweight mesh OR polypropylene mesh).

Quality assessment, data extraction and data analysis adhered to the PROSPECT methodology [7]. Pain intensity scores were used as the primary outcome measure. In this study, we defined a change of more than 10 mm on the visual analogue scale (VAS) or numerical rating score (NRS) as clinically relevant (8). The effectiveness of each intervention

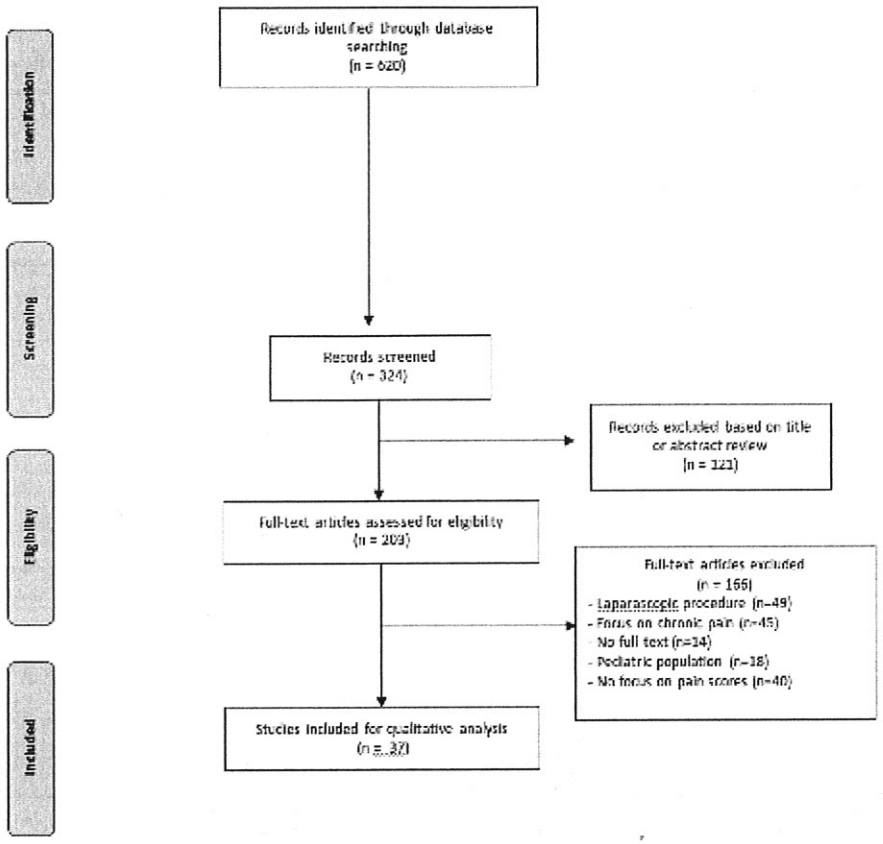


Fig. 1. — PRISMA flow diagram of studies.

for each outcome was evaluated qualitatively by assessing the number of studies showing a significant difference between treatment arms ($p < 0.05$ as reported in the study publication). A meta-analysis was not performed due to heterogeneity in study design and result reporting, restricting pooled analysis.

Recommendations were made according to PROSPECT methodology (7). In brief, this involved a grading of A–D according to the overall level of evidence, as determined by the quality of studies included, consistency of evidence and study design. The proposed recommendations were sent to the PROSPECT Working Group for review and comments and a modified Delphi approach was utilised as previously described. Once a consensus was achieved the lead authors drafted the final document, which was ultimately approved by the Working Group.

Results

PRISMA flow chart demonstrating the search data are presented in Figure 1. The methodological quality assessments of the 38 RCTs included for the final qualitative analysis are summarized in Table S1. The characteristics of the included studies are shown in Table S2 and Table S3.

Systemic non-opioid analgesics

One placebo-controlled RCT (n=50) reported gabapentin (400 mg) prior to surgery reduced pain scores and postoperative morphine requirements in the immediate postoperative period. No obvious side-effects were reported (9). Another placebo-controlled RCT (n=60) reported that preoperative gabapentin (1200 mg) significantly reduced pain scores (at rest and on sitting) and reduced the total tramadol consumption at 8, 12, 16, 20 and 24 hours after surgery (10). Pain scores at 1, 3 and 6 months after surgery were lower in the gabapentin group than in the placebo group (10). A large placebo-controlled RCT (n=425) found that preoperative pregabalin (50, 150, or 300 mg/day) as adjuvant analgesic did not influence the intensity of postoperative pain at 24 hours (11). Of note, there was a wide variability in the anesthetic and analgesic techniques.

One placebo-controlled RCT (n=77) found no statistical significant difference in pain during the first 24 hours, postoperatively with a TNF-α inhibitor, etanercept 50 mg, administered subcutaneously 90 min before incision (12).

A placebo-controlled RCT (n=55) evaluated the effects of rofecoxib 50 mg (a COX-2 selective

Table S1

Quality assessment and level of evidence assigned to the randomised trials included in the review for analgesia after inguinal hernia repair surgery

Study	Allocation concealment: A-D	Jadad Score	Statistical analyses and patient follow-up	Level of Evidence
Mahoori A et al 2014 (9)	A	3	no	1
Sen H et al 2009 (10)	A	3	no	1
Singla NK et al 2014 (11)	A	4	no	1
Cohen SP et al 2013 (12)	A	5	yes	1
Schurr M et al 2009 (13)	A	3	no	1
Somri M et al 2017 (14)	A	5	yes	1
Kang H et al., 2011 (15)	A	4	no	1
Chaparro LE et al 2012 (16)	A	5	yes	1
Mentes O et al 2009 (17)	A	4	no	1
Viscusi E et al 2019 (18)	A	5	yes	1
Velanovich V et al 2019 (19)	A	5	yes	1
Neisioonpour SH et al 2013 (20)	A	3	no	1
Santos SC et al., 2011 (21)	C	3	no	2
Saeed M et al., 2015 (22)	C	4	no	2
Baerentzen F et al., 2012 (23)	A	4	no	1
Vizcaino-Martinez L et al 2014 (24)	A	3	yes	1
Aveline C et al 2011 (25)	A	5	no	1
Okur O et al 2017 (26)	A	3	yes	1
Hosalli V et al 2019 (27)	A	5	yes	1
Theodoraki K et al 2019 (28)	A	5	yes	1
Wegner R et al 2017 (29)	A	5	no	1
Razavizadeh MR et al 2017 (30)	B	4	no	1
Akyol BC et al 2018 (31)	A	3	yes	2
Heil JW et al 2014 (32)	A	4	no	1
Bhattacharya P et al 2010 (33)	A	4	no	1
Magnusson J et al 2016 (34)	A	3	yes	1
Kingsnorth A et al 2012 (35)	A	3	no	1
Manyilirah W et al 2012 (36)	A	4	yes	1
Gundre NP et al 2012 (37)	A	2	no	1
Torcivia A et al 2011 (38)	A	1	no	1
Canonico S et al 2013 (39)	B	3	no	1
Fan JKM et al 2017 (40)	A	5	yes	1
Carro JLP et al 2017 (41)	B	3	yes	1
Bracale V et al 2014 (42)	A	2	no	1
Shen YM et al 2012 (43)	A	2	no	1
Bona S et al 2018 (44)	A	3	yes	2
Hoyuela C et al 2016 (45)	A	5	yes	1

inhibitor that has been withdrawn from the market due to potential cardiac complications) given one hour pre-operatively followed by once daily for 4 days after surgery (13). Rofecoxib reduced pain scores on the first postoperative day, but the opioid requirements remained similar to the placebo group. A placebo-controlled RCT (n=60) evaluated the effects of oral etoricoxib 120 mg given 1 hour preoperatively (14). Pain scores at rest and on straight leg raise were significantly lower in the etoricoxib group at 16 and 24 hours, and on discharge.

A placebo-controlled RCT (n=64) assessed the effects of intra-operative intravenous bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion (2 mg/kg/h) (15). Fentanyl consumption was significantly lower in the lidocaine group until

Table S2

Summary of key results from studies evaluating systemic analgesics, analgesics adjuncts, regional anesthesia, and surgical procedures used to support the recommended interventions in patients after open inguinal hernia repair

Study	Study design	Pain Scores	Cumulative opioid dose	Baseline Analgesia
Pre-operative				
Systemic non-opioid analgesics				
Schurr M et al. 2009 (13)	Rofecoxib 50 mg or placebo 1 hour prior to surgery and once daily on postoperative day 1-4.	Significantly lower ratings for least pain in patients with COX-2 inhibitor intake on the operative day.	No difference in milligrams hydrocodone bitartrate consumed.	Patients were given hydrocodone bitartrate as needed postoperative.
Somri M et al. 2017 (14)	Etoricoxib 120 mg or placebo 1 hour preoperative.	Significantly lower pain scores in patients with COX-2 inhibitor at 16, 24 h and on discharge, in rest and with active straight leg raise.	Amount of rescue analgesic doses of morphine (mg) within 24 h were significantly lower in COX-2 inhibitor group.	When VAS≥4 at PACU 1-3mg boluses of morphine were used until a response of 1 on a verbal point descriptive scale of 5 was achieved.
Intra-operative				
Topical and surgical site infiltration with extended-release local anesthetics				
Nesioonpour SH et al. 2013 (20)	Wound infiltration prior to incision infiltrated by the surgeon. One group received 10 ml of bupivacaine 0.5% and the control group placebo (10 ml normal saline).	Mean pain score at all time points (every 4 h during 24 h postoperative) were lower in the treatment group.	The amount of opioid use for the bupivacaine group was 80% less in the first 24 h.	If NRS pain score > 4 intravenous admission of 15 mg pethidine was injected.
Ilio-inguinal and ilio-hypogastric nerve block				
Santos SC et al. 2011 (21)	Ilioinguinal and Iliohypogastric nerve block with 10 mL of 0.75% ropivacaine, and wound infiltration with 10 mL of 0.75% ropivacaine versus no block nor wound infiltration	Visual analogue scale at rest was significant lower 3 h after surgery. No difference at 6 and 12 h after surgery and with movement.	Not mentioned.	VAS > 4 received intravenous dipyrone (2.0 g). In case ineffective, intravenous ketorolac (30 mg) and, whenever necessary, intravenous nalbuphine (3 mg), were added.
Saeed M et al. 2015 (22)	Iliohypogastric and ilioinguinal block (12ml 0.75% ropivacaine) and incision infiltration prior to incision.	Median VAS was lower in the intervention group.	Not mentioned, only time for demand first dose analgesia	VAS>3, on demand paracetamol 1000mg and if necessary 75 mg diclofenac sodium.
Baerentzen F et al. 2012 (23)	Ilio-hypogastric and ilio-inguinal block with 20 mL bupivacaine 0.5% or a placebo block with 20 ml saline.	Significant lower pain scores at mobilization and rest upon arrival in PACU and after 30 minutes.	No significant difference between the two groups.	/
TAP-block				
Aveline C et al. 2011 (25)	Ultrasound-guided TAP block (levo-bupivacaine 0.5%, 1.5mg/kg) versus blind IH block (levobupivacaine 0.5%, 1.5mg/kg) before surgery.	Vas pain scores at rest were lower in the US-guided TAP group at 4h, 12h and 24h.	No significant difference.	Paracetamol 1000 mg and keto-profen 100 mg i.v. during surgery. At PACU 3 mg i.v. morphine boluses at 5 min intervals, until VAS ≤3.
Okur O et al. 2017 (26)	TAP block versus ilio-hypogastric and ilio-inguinal nerve block versus no block. Blocks were done with 20 ml of 0.25% isobaric bupivacaine.	Pain scores were significantly lower at all time points of the study groups versus placebo. Only at 24 h there was a significantly difference between TAP and IHIN in favor of TAP.	No significant difference in additional analgesic requirement was found between study groups.	Acetaminophen 10–15 mg/kg once every 6 h and salvage analgesia of intravenous tramadol hydrochloride 50 mg.
Hosalli V et al. 2019 (27)	Dual TAP-block and ilioinguinal/ iliohypogastric block versus ilioinguinal/ iliohypogastric block.	VAS at 12, 24 and 48 h were significantly lower in Dual TAP-group compared to IL/IH group alone.	A higher number of patients required rescue analgesics in IL/IH group.	Fentanyl 0.5 µg/kg and, after 2 h if the pain persists (VAS score of ≥4 at rest) even after giving fentanyl intravenous tramadol 50 mg added.
Theodoraki K et al. 2019 (28)	TAP-block (ropivacaine 0.75% 20ml) versus placebo (saline 20ml)	Significant different pain scores in favour of TAP-block in rest at 6 and at 24 h. For movement at 3, 6 and 24 h postoperatively.	Lower median morphine consumption via the PCA device for the first 24 h in comparison to the placebo group.	Paracetamol 1g and parecoxib 40mg intravenously 30min approximately before the end of surgery.
Razavizadeh MR et al. 2017 (30)	Addition of dexamethasone 8 mg to epidural block into epidural space versus placebo (saline 2ml).	Onset/duration of anesthesia was significantly more rapid and longer in the dexamethasone group.	Not mentioned.	Not mentioned.
Post-operative				
TAP-block				
Akyol BC et al. 2018 (31)	Intravenous analgesic regimen (group I) versus subcostal TAP-block postoperatively in addition to an intravenous analgesic regimen (group II)	Pain scores significantly lower in group II compared with group I: postoperative 15th-minute; 1st-, 6th-, 12th-, and 24th-hour; 15th-day and 1st-month NRS values.	NRS-score > 4 received an additional dose of 1 mg/kg tramadol IV.	During close-up of the surgery, patients in both groups were given 100mg tramadol and 1000mg paracetamol IV.

NS = no significant difference between groups, POD = Postoperative Day.

Table S3

Summary of key results from studies evaluating systemic analgesics, analgesics adjuncts, regional anesthesia, and surgical procedures used to support the NOT recommended interventions in patients open inguinal hernia repair surgery

Study	Study design	Pain Scores	Cumulative opioid dose	Baseline analgesia
Pre-operative				
Systemic non-opioid analgesics				
Gabapentinoids				
Mahoori A et al. 2014 (9)	Gabapentin 400 mg versus placebo 2 h prior to herniorraphy	Reduced pain scores postoperative at 2, 4, 12 h and 24 h	Reduced postoperative morphine requirements	Morphine 0.05 mg/kg intravenously on demand
Sen H et al. 2009 (10)	Gabapentin 1200 mg or placebo 1 hour prior to surgery	Gabapentin group had signifi-cantly lower VAS scores at time 1, 4, 8, 12, 16, 20 and 24 h post-operative and also at 1,3 and 6 months postoperative	Tramadol consumption was lower at time 8, 12, 16, 20 and 24 h postoperative.	PCA device postoperative with bolus of tramadol 20 mg (lockout interval 15 min and a 4 hour maximal dose of 150 mg) VAS>4 were given 75mg diclofenac intramuscular
Singla NK et al. 2014 (11)	Pregabalin 50, 150 or 300 mg/day or placebo 12 and 2 h prior to surgery and once daily 1 week postoperative	No statistically significant difference in pain scores between 300 mg/day pregabalin and placebo	Decreased by 41% and by 59% in patients receiving 150 and 300 mg/day pregabalin, respectively, when compared with placebo	500 mg naproxen (bid) for 3 days. 50 mg tramadol and 500–650 mg acetaminophen every 4 h, as needed. if still inadequate, 5 mg oxycodone every 4 h, as needed.
TNF-alpha inhibitor				
Cohen SP et al. 2013 (12)	Etanercept 50 mg subcutaneous or placebo 90 minutes prior to surgery.	The NRS pain scores were lower in the etanercept group though these results were not statistically significant.	Etanercept group required less opioids (morphine) though not statistically significant.	Morphine as needed post-operative.
Intra-operative				
Systemic non-opioid analgesics				
Lidocaine				
Kang H et al. 2011 (15)	Intravenous bolus injection of 1.5 mg/kg lidocaine followed by a continuous lidocaine infusion of 2 mg/kg/h.	VAS pain scores in the lidocaine group were significantly lower at 2, 4, 8 and 12 h after surgery.	Total fentanyl consumption (PCA and rescue admi-nistration was significantly lower in the lidocaine group.	PCA infusion of 0.1 µg/kg/h fentanyl and on-demand release of a 0.1 µg/kg bolus. When VAS>3 50 µg of fentanyl was administered.
Dipyrone				
Chaparro LE et al. 2012 (16)	Dipyrone 15mg vs Dipyrone 40mg intravenously after induction	D15 group, the D40 group showed a lower incidence of moderate to severe pain only in the first 30 minutes.	There was more morphine consumption in the D15 group.	Not mentioned.
Topical and surgical site infiltration with extended-release local anesthetics				
HTX-011				
Viscusi E et al. 2019 (18)	Near completion surgery local infiltration with HTX-011 300 mg/9 mg (bupivacaine/meloxicam) or bupivacaine HCl 0.25%, 75 mg or saline placebo.	HTX-011 significantly reduced mean pain intensity by 23% versus placebo. A significant reduction of 21% for pain intensity over 72 h of HTX-011 compared to bupivacaine.	Opioid consumption over 72 h was reduced by 38% versus placebo and 25% versus bupivacaine HCl.	As needed: oral oxycodone (10mg max/4h), and/or IV morphine as needed(10mg max/2h), and/or oral acetaminophen (1000mg max/6h).
INL-001				
Velanovich V et al. 2019 (19)	Comparison of INL-001 (implant designed to provide extended delivery of bupivacaine to the area around the surgical wound) with placebo implant.	Patients who received INL-001 reported lower pain intensity through 72 h.	Less opioid analgesic usage in the INL-001 group compared throughout the first 24 h in both studies	Postoperative parenteral morphine as needed.
Ilio-inguinal and ilio-hypogastric block				
izcaino-Martinez L et al. 2014 (24)	General anesthesia with ilioinguinal nerve block versus spinal anesthesia alone	Only significant 2 h after admission and before discharge. Analgesic drug significantly bigger in spinal anesthesia group.	Not mentioned.	Paracetamol (1 g/8 h), metamizol (2 g/8 h), dexketoprofen (50 mg/8 h) and fentanyl (bolus of 25 µg/15 min i.v.) until VAS<3.
TAP-block				
Wegner R et al. 2017 (29)	Dexamethasone 8 mg added to ropivacaine TAP-block.	The dexamethasone had a greater change in pain score though no statistical significant difference was noted.	Not mentioned.	Not mentioned.
Heil JW et al. 2014 (32)	Continuous TAP-block (catheter 2 days postoperative) with Ropivacaine 0.5% 20ml bolus initially versus saline injection.	Not significant	Not significant.	Intravenous fentanyl was administered at PACU at need.
Anesthetic technique				
Bhattacharya P et al. 2010 (33)	Unilateral lumbar PVB versus conventional spinal anesthesia	No statistical significant difference.	Only the time to first postoperative analgesic require-ment was longer in the PVB group.	VAS scores of 4 or more were treated with rescue analgesic tramadol in boluses of 50mg i.v.

Surgical technique				
Magnusson J et al. 2016 (34)	UltraPro Hernia System, versus Prolene Hernia System versus Lich-tenstein hernia repair.	NS.	Not mentioned.	Not mentioned.
Kingsnorth A et al. 2012 (35)	Sutureless Parietex™ ProGrip™ mesh repair versus traditional Lichtenstein repair with lightweight polypropylene mesh secured with sutures.	Pain score was lower in the parietex™ group at discharge and at 7 days postoperative.	Not mentioned.	Not mentioned.
Manyilirah W et al. 2012 (36)	Comparison of non-mesh (Desarda) and mesh (Lichtenstein) technique for open inguinal hernia repair.	There was no significant difference 1-2 h postoperative and not after 3 days.	Not mentioned.	Not mentioned.
Gundre NP et al. 2012 (37)	Polyethylene vs polypropylene mesh	The mean average post-operative pain was similar between groups	Not mentioned.	Not mentioned.
Torcivia A et al. 2011 (38)	Glucamesh® vs Polypropylene®	On the evening of the intervention the pain was less intense in the Glucamesh® group.	Not mentioned	Not mentioned.
Canonico S et al. 2013 (39)	Lightweight, large-pore mesh vs heavy weight mesh with small pores	Patients with lightweight, large-pore mesh reported less pain postoperative.	Not mentioned.	Not mentioned.
Fan JKM et al. 2017 (40)	Self gripping semi reabsorbable mesh (Progrip) vs polypropylene mesh.	No significant pain differences at any time point.	Not mentioned	Not mentioned.
Carro JLP et al. 2017 (41)	Low density vs high density Mesh	Only on the 1st postoperative day and the 7th postoperative day).	Not mentioned.	Not mentioned.
Bracale V et al. 2014 (42)	Fibrin glue vs Lichtenstein fixation of Mesh	Postoperative pain was lower in the fibrin glue group at 1 week and 1 month.	Patients requiring analgesics in the fibrin glue group were significantly less.	Not mentioned.
Shen YM et al. 2012 (43)	NBCA (n-butyl-2-cyanoacrylate) medical adhesive vs traditional suture	24 h after surgery VAS was significant lower in the NBCA-group when compared with the control group.	Not mentioned.	Not mentioned.
Bona S et al. 2018 (44)	Lightweight mesh (Ultrapro®) vs heavyweight mesh (Prolene®) in patients with primary inguinal hernia repair (Lichtenstein technique)	A statistically significant difference in favour of lightweight mesh for pain at 1 week and 6 months after surgery	NS.	NS.
Hoyuela C et al. 2016 (45)	Glue (Histoacryl®) or non-absorbable polypropylene sutures for fixation of lightweight polypropylene mesh.	Postoperative pain at 8 h, 24 h, 7 days and 30 days was less when glue was used instead of sutures for all measures.	Not mentioned.	All patients received paracetamol 1000 mg eyery 8h and dexketoprofen 25 mg every 8h for 7 days.
Post-operative				
Systemic non-opioid analgesics				
Mentes O et al. 2009 (17)	Lornoxicam 8 mg at the end of surgery and 12 h after versus tramadol 1 mg/kg at the end of surgery and every 6 h up to 24 h postoperative.	No statistical significant difference in the effect of pain 12 h and 24 h after surgery.	Patients were not receiving rescue analgesia protocol.	Study protocol.

NS = no significant difference between groups, POD = Postoperative Day.

12 hours after surgery after which the difference became insignificant. Another RCT (n=162) evaluated the effects of intra-operative dipyrone 15 mg/kg or 40 mg/kg IV during the operation (16). A statistically significant difference was only found during the first 30 minutes in the PACU. One RCT (n=160) reported no difference in pain scores 12 and 24 hours after surgery, between lornoxicam (an NSAID administered at the end of the operation and 12 hours post-operatively) and tramadol (17). However, the tramadol group experienced more nausea.

Local/Regional Analgesia Techniques

Topical and surgical site infiltration with extended-release local anesthetics

One placebo-controlled RCT (n=418) showed a significant reduction in pain with the use of HTX-011 (a novel, extended release, fixed-dose combination local anesthetic comprising bupivacaine and low-dose meloxicam, incorporated in a proprietary Biochronomer® polymer) (18). It showed a 23% reduction in mean pain intensity over 72 hours compared to placebo. At all timepoints through 72 hours, the mean pain scores were lower in the HTX-011 group. A reduction of 21% for pain intensity over 72 hours was observed when HTX-011 was compared to plain bupivacaine. Of note, basic analgesics – paracetamol and/or NSAIDs were not used.

One study, which consisted of two RCTs (n=417), compared the effect of INL-001 (an implant designed to provide extended delivery of bupivacaine to the area around the surgical wound) with placebo implant (19). Patients who received INL-001 reported lower pain intensity through 72 h for the two pooled studies. One placebo-controlled RCT (n=60) in patients receiving spinal anesthesia

examined the effects of wound infiltration with bupivacaine 0.05% 10 mL prior to incision (20). Early postoperative pain was significantly lower at all timepoints in favour of the bupivacaine group.

Ilio-inguinal and ilio-hypogastric block

A placebo-controlled RCT (n=34) investigated the possible benefits of an additional ilio-inguinal, ilio-hypogastric block (10mL 0.75% ropivacaine) and surgical wound infiltration (10mL 0.75% ropivacaine) (21). Pain scores were lower in the control group 3 hours post-surgery. There was no difference in pain scores at 6 and 12 hours post-surgery. Another placebo controlled RCT (n=60) found that an ilio-inguinal and ilio-hypogastric block (12mL 0.75% ropivacaine) and wound infiltration prior to incision provided significantly lower median VAS scores compared with placebo (22). A placebo-controlled RCT (n=60) also investigated the effects of ultrasound-guided ilioinguinal and ilio-hypogastric nerve blocks. A significant reduction in pain scores at mobilization and rest was recorded in the bupivacaine group vs placebo upon arrival in the post anesthesia care unit (PACU) and again after 30 minutes. However, opioid consumption was not significantly different between groups (23). Yet another RCT (n=32) investigated general anesthesia combined with ilio-inguinal nerve block vs spinal anesthesia alone. Except for the first 2 h after surgery, there was no difference in pain scores for the 24 h study period (24).

Transversus abdominis plane (TAP) blocks

A RCT (n=273) compared ultrasound-guided TAP block (levobupivacaine 0.5%, 1.5mg/kg) with blind ilio-hypogastric and ilio-inguinal block (levobupivacaine 0.5%, 1.5mg/kg) performed before surgery. Pain at rest was lower during the first 24h after ultrasound-guided TAP block, but this difference was not observed during movement (25). Okur et al. (n=90) found that pain scores with TAP block were significantly lower at 24 h compared with ilio-inguinal-ilio-hypogastric blocks in a post-hoc analysis (26). A prospective RCT (n=197) compared the effects of ultrasound-guided TAP block combined with Ilio-inguinal/Ilio-hypogastric nerve blocks vs Ilio-inguinal/Ilio-hypogastric nerve blocks alone. Pain scores at 12, 24 and 48 hours were significantly lower in the TAP block and ilio-inguinal/ilio-hypogastric block group compared to Ilio-inguinal/Ilio-hypogastric nerve block alone (27).

Theodoraki et al. compared the effects of an US-guided TAP block with ropivacaine vs an US-guided TAP block with saline and concluded that pain was reduced with a ropivacaine TAP block (28). Statistical significant differences were noted at rest, at 6 and 24 hours and with movement at 3, 6 and 24 hours, in favour of TAP block (28).

A placebo-controlled RCT (n=82) found no significant difference between the adjuvant effect of dexamethasone to ropivacaine in TAP blocks (29). Another placebo-controlled RCT (n=44) investigated the effect of adding dexamethasone 8 mg to a lumbar epidural anesthesia block. The onset of epidural anesthesia, the primary outcome of this study, was significantly more rapid in the dexamethasone group than in the control group. The duration of analgesia was markedly prolonged in the dexamethasone group than in the control group (30).

Another RCT (n=100) compared the effect of a post-operative subcostal TAP block to a standard analgesic regimen. At different timepoints after surgery (15 min, 1 h, 6 h, 12 h, 24 h ; 15 days and one month) there was a significantly difference in pain scores between the two groups in favour of the TAP block group (31).

One randomized triple-masked, placebo-controlled study (n=20) investigated the effects of single injection TAP block vs a continuous TAP block through a perineural catheter for 2 days post-operative (32). There were no differences between a single injection and continuous infusion at 6, 24, 48 and 72 hours after surgery. However, this study was underpowered.

Anesthetic technique

One placebo-controlled RCT (n=58) study found no difference in pain scores at 2, 12 and 24 hours between spinal anesthesia and paravertebral block (PVB). Of note, these techniques had a 7% failure rate (33).

Surgical technique

One placebo-controlled RCT (n=309) compared Lichtenstein technique with Prolene Hernia System (PHS) and UltraPro Hernia System (UHS). There were no differences between groups regarding perioperative course, operating time, postoperative pain or rehabilitation (34). Pain was assessed daily until 14 days postoperatively by a research nurse using a telephone interview. Need time points for pain assessments. A placebo-controlled RCT (n=302) used Sutureless Parietex™ ProGrip™

mesh repair vs traditional Lichtenstein repair with lightweight polypropylene mesh secured with sutures. The pain scores were significantly lower in the sutureless mesh group at discharge and at 7 days, but not at 1 month after surgery (35). One RCT (n=101) evaluated the effects of non-mesh (Desarda) vs mesh (Lichtenstein) methods for inguinal hernia repair. No differences in terms of postoperative pain between the two techniques were noted (36). There was no significant difference in pain scores at 1-2 hours postoperative and after 3 days.

Another placebo-controlled RCT (n=70) found no significant differences in early postoperative pain, infection, seroma, recurrence and other complications between different types of mesh (37). However, this study might be underpowered. Another placebo-controlled RCT (n=50) comparing Glucamesh® vs Polypropylene® mesh found that the pain scores (measured twice daily for 7 post-operative days) were significantly lower before discharge in the glucamesh group (38).

A placebo-controlled study (n=80) evaluated the effect of sutureless fixation with fibrin glue of lightweight mesh in open inguinal hernia repair. Patients in the lightweight group reported less pain during the first month after surgery (39). Another placebo-controlled RCT (n=45) found no differences in pain scores between self-gripping mesh vs polypropylene mesh (40). In a comparison between low density vs high density mesh, there were differences in pain scores only on the 1st and the 7th postoperative days in favour of low density mesh (41). One randomized controlled trial (n=102) compared the effect of fibrin glue vs Lichtenstein mesh repair (42). The fibrin group had lower pain scores and opioid requirements at 1 week. A randomized controlled trial (n=110) compared fibrin glue as medical adhesive NBCA (n-butyl-2-cyanoacrylate) vs suture for patch fixation in Lichtenstein inguinal herniorrhaphy (43). The pain scores in the fibrin group were lower at 24 hours after surgery. One multicenter RCT (n=808) compared the effects of lightweight mesh (Ultrapro®) vs heavyweight mesh (Prolene®), and reported lower postoperative pain scores in favour of lightweight mesh (44). One multicenter RCT (n=370) compared the effects of glue (Histoacryl®) or non-absorbable polypropylene sutures for fixation of lightweight polypropylene mesh (45). Postoperative pain was less in the group where glue was used.

Discussion and conclusion

The majority of the studies included in this systematic review were determined to be of high quality and all but three showed statistically significant results. The updated literature strengthens the previous PROSPECT recommendations for pain management in patients undergoing open IHR (5). The updated PROSPECT methodology further strengthens the recommendations, because it goes beyond assessment of the available evidence based solely on the simple statistical analysis (7).

Table 1

Overall recommendations for pain management in patients undergoing open inguinal hernia repair

Pre-operative and intra-operative
• Paracetamol (Grade D)
• Cyclo-oxygenase-2 selective inhibitor (Grade D)
• Intravenous dexamethasone (Grade B)
• Local anesthetic infiltration and/or regional analgesia (ilio-inguinal/ilio-hypogastric nerve block or transversus abdominis plane block)
Postoperative
• Paracetamol (Grade D)
• Cyclo-oxygenase-2 selective inhibitor or non-steroidal anti-inflammatory drugs (Grade D)
• Opioid for rescue (Grade D)
Anesthetic technique
• Field block (e.g., ilio-inguinal/ilio-hypogastric block) with or without wound infiltration as a sole anesthetic or as an adjunct to general anesthesia (Grade A)
Surgical technique
• Mesh techniques in preference to non-mesh techniques (Grade A)

Combination of basic analgesics such as paracetamol and NSAID or COX-2 selective inhibitor along with a local/regional analgesic techniques (e.g., local infiltration with or without a field blocks such as ilio-inguinal/ilio-hypogastric nerve block or interfascial plane blocks such as TAP block) is recommended pre-operatively and/or intra-operatively. Paracetamol and NSAID have been shown to provide excellent analgesia and reduce opioid requirements, and should be continued in the postoperative period, with opioids used as rescue analgesics (Table 1). Although wound infiltration is recommended, the role of extended release local anesthetics, topical NSAIDs, clonidine, dexamethasone, or opioids remain controversial.

With regards to the choice of anesthetic technique, the current systematic review strengthens our previous recommendation of using a field block (e.g., ilio-inguinal/ilio-hypogastric block) with or without wound infiltration as a sole anesthetic or as an adjunct to general anesthesia. In fact, even the recent International guidelines recommend the use of local anesthesia provided the surgeon is experienced in this technique (1). Obviously, patient selection and acceptance to a sole regional/local

Table 2

Analgesic interventions that are not recommended for pain management in patients undergoing open inguinal hernia repair

	Intervention	Reason for not recommending
Pre-operative	Gabapentinoids	Conflicting procedure-specific evidence
	Clonidine	Insufficient procedure-specific evidence
	Ketamine	Insufficient procedure-specific evidence
	Etanercept	Insufficient procedure-specific evidence
	Epidural analgesia	Although effective these techniques are relatively invasive with potential for complications
	Paravertebral blocks	Although effective these techniques are relatively invasive with potential for complications
Intra-operative	Psoas block	Insufficient procedure-specific evidence
	Wound infiltration with extended release bupivacaine	Insufficient procedure-specific evidence
	Wound infiltration using conventional non-steroidal anti-inflammatory drugs , clonidine or opioids	Insufficient procedure-specific evidence
	Topical non-steroidal anti-inflammatory drugs	Insufficient procedure-specific evidence
	Intravenous lidocaine infusion	Insufficient procedure-specific evidence
	Topical extended-release local anesthetic	Limited procedure-specific evidence
Postoperative	Transcutaneous Electrical Nerve Stimulation	Limited procedure-specific evidence
	Compressive cryotherapy or ice wrapping	Lack of procedure-specific evidence
Surgical technique	Zolpidem as a sleep aid	Limited procedure-specific evidence
	Nerve section	Limited of procedure-specific evidence
	Cryoanalgesia techniques	Insufficient procedure-specific evidence
	TENS	Inconclusive procedure-specific evidence

anesthetic is imperative. A recent meta-analysis of RCTs comparing local anesthesia vs other forms of anesthesia (including general anesthesia) concluded that local anesthesia allows shorter operating room times and is associated with lower incidence of urinary retention (compared with neuraxial anesthesia) (46). Also, patient satisfaction with local anesthesia was similar to that with other anesthetic techniques (46). Although in comparison with general anesthesia, neuraxial block is associated with reduced pain scores and decreased post-operative analgesic requirement, their use is associated with side effects (e.g., postural hypotension) that might delay recovery and discharge home in a day care setting.

It is recommended that the surgical technique should be based on surgeon's expertise, hernia-related characteristics, and availability of local resources (1). Nevertheless, as far as postoperative pain is concerned, a mesh technique is in preference to non-mesh techniques. This recommendation is also validated by the International guidelines for groin hernia management (1).-

Several analgesic interventions are not recommended due to either conflicting data, insufficient data, or lack of evidence (Table 2). These include analgesic adjuncts such as gabapentinoids, clonidine, corticosteroids, ketamine, intravenous lidocaine infusion, and etarnacept. Neuraxial analgesic techniques (epidural or paravertebral analgesia) are not recommended despite the fact that they provide excellent pain relief because they are invasive and have potential complications. Psoas-block is not recommended at the moment due to insufficient evidence. However, newer interfascial plane blocks such as erector spinae blocks may provide pain relief and negate the concerns of neuraxial blocks (47). However, evidence currently is lacking for open inguinal hernia repair.

The limitations in this review are related to those of the included studies. There was considerable heterogeneity between studies with regards to dosing regimens and route of administration as well as timing of pain assessments. The small size of most studies has the potential for estimation effect and do not provide safety profile of the analgesic interventions. In a majority of the studies the analgesic intervention was not evaluated against an optimized multimodal analgesic regimen.

In summary, this review has identified an

analgesic regimen that for optimal pain management after open inguinal hernia repair as well as interventions that are not recommended for pain management in patients undergoing IHR. Future adequately powered studies should assess the effects of analgesic interventions not only on pain, opioid consumption, opioid-related adverse events and complications associated with the intervention, but also outcome measures such as time to ambulation, length of hospital stay, and the occurrence of chronic pain or chronic opioid consumption. Furthermore, the influence of analgesic intervention on patient-specific factors such as chronic pain and chronic opioid therapy need to be assessed.

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