

PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations.

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Publication year: 2021

Journal: Anaesthesia

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Society: PROSPECT

Origin country: Belgium

Target countries: International

DOI: 10.1111/anae.15339

PMID: 33370462

Source: <https://pubmed.ncbi.nlm.nih.gov/33370462/>

Anaesthesia Anaesthesia 379 blackwellopen 0370524 ANAE Anaesthesia 0003-2409 1365-2044 pmc-is-collection-domain yes pmc-collection-title Wiley Open Access Collection PMC8048441 PMC8048441.1 8048441 8048441 33370462 10.1111/anae.15339 ANAE15339 1 Guidelines Guidelines PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations Guidelines for pain management after caesarean section Roofthoof et al. Roofthoof E. Consultant/PhD Student 1 2 Joshi G. P. Professor 3 Rawal N. Professor 4 Van de Velde M. Professor and Chair 5 marc.vandavelde@uzleuven.be @MarcVandeVelde6 the PROSPECT Working Group* of the European Society of Regional Anaesthesia and Pain Therapy and supported by the Obstetric Anaesthetists' Association Joshi G. P. Pogatzki-Zahn E. Van de Velde M. Schug S Kehlet H Bonnet F Rawal N Delbos A Lavand'homme P. Beloeil H Raeder J Sauter A Albrecht E Lirk P Lobo D Freys S * 1 Department of Anesthesiology GZA Sint-Augustinus Hospital Antwerp Belgium 2 Department of Cardiovascular Sciences KU Leuven and UZ Leuven Leuven Belgium 3 Department of Anesthesiology and Pain Management University of Texas Southwestern Medical Center Dallas Texas USA 4 Department of Anesthesiology Orebro University Orebro Sweden 5 Department of Cardiovascular Sciences KU Leuven and UZ Leuven Leuven Belgium * Correspondence to: M. Van de Velde Email: marc.vandavelde@uzleuven.be * Members of the PROSPECT Working Group, see Appendix 1 .

28 12 2020 5 2021 76 5 379788 10.1111/anae.v76.5 665 680 05 11 2020 15 04 2021 16 04 2021 17 04 2021 © 2020 The Authors. Anaesthesia published by John Wiley & Sons Ltd on behalf of Association of Anaesthetists. <https://creativecommons.org/licenses/by-nc/4.0/> This is an open access article under the terms of the <http://creativecommons.org/licenses/by-nc/4.0/> License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. Summary Caesarean section is associated with moderate to severe postoperative pain, which can influence postoperative recovery and patient satisfaction as well as breastfeeding success and mother-child bonding. The aim of this systematic review was to update the available literature and develop recommendations for optimal pain management after elective caesarean section under neuraxial anaesthesia. A systematic review utilising procedure-specific postoperative pain management (PROSPECT) methodology was undertaken. Randomised controlled trials published in the English language between 1 May 2014 and 22 October 2020 evaluating the effects of analgesic, anaesthetic and surgical interventions were retrieved from MEDLINE, Embase and Cochrane databases. Studies evaluating pain management for emergency or unplanned operative deliveries or caesarean section performed under general anaesthesia were excluded. A total of 145 studies met the inclusion criteria. For

patients undergoing elective caesarean section performed under neuraxial anaesthesia, recommendations include intrathecal morphine 50–100 µg or diamorphine 300 µg administered preoperatively; paracetamol; nonsteroidal anti-inflammatory drugs; and intravenous dexamethasone administered after delivery. If intrathecal opioid was not administered, single injection local anaesthetic wound infiltration; continuous wound local anaesthetic infusion; and/or fascial plane blocks such as transversus abdominis plane or quadratus lumborum blocks are recommended. The postoperative regimen should include regular paracetamol and nonsteroidal anti-inflammatory drugs with opioids used for rescue. The surgical technique should include a Joel-Cohen incision; nonclosure of the peritoneum; and abdominal binders. Transcutaneous electrical nerve stimulation could be used as analgesic adjunct. Some of the interventions, although effective, carry risks, and consequentially were omitted from the recommendations. Some interventions were not recommended due to insufficient, inconsistent or lack of evidence. Of note, these recommendations may not be applicable to unplanned deliveries or caesarean section performed under general anaesthesia.

pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes
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source-schema-version-number 2.0 cover-date May 2021 details-of-publishers-converter
Converter:WILEY_ML3GV2_TO_JATSPMC version:6.0.2 mode:remove_FC converted:15.04.2021
This article is accompanied by an editorial by Landau and Richebé, *Anaesthesia* 2021; 76: 587–9.

Implement strategies to minimise systemic opioid utilisation and develop individualised or stratified postdischarge opioid prescribing practices to reduce unnecessary opioid analgesic consumption after elective caesarean section.

Add intrathecal morphine 50–100 µg or diamorphine 300 µg to spinal anaesthesia. Epidural morphine 2–3 mg or diamorphine 2–3 mg may be used as an alternative, for example, when an epidural catheter is used as part of a combined spinal-epidural technique.

Prescribe paracetamol and a nonsteroidal anti-inflammatory drug (NSAID) administered after delivery and continued regularly postoperatively.

Administer a single dose of intravenous (i.v.) dexamethasone after delivery in the absence of contraindications.

Consider a single injection of local anaesthetic infiltration, continuous wound local anaesthetic infusion and/or fascial plane blocks, if intrathecal morphine is not used.

Use a surgical technique that includes the Joel-Cohen incision, nonclosure of the peritoneum and abdominal binders.

Consider the use of transcutaneous electrical nerve stimulation as an analgesic adjunct.

Caesarean section is associated with moderate-to-severe postoperative pain which may influence recovery, psychological maternal well-being, breastfeeding and mother-child bonding. The aim of this guideline is to provide clinicians with updated evidence for optimal pain management following elective caesarean section under neuraxial anaesthesia.

The procedure-specific postoperative pain management (PROSPECT) recommendations for pain management after caesarean section were published in 2014; however, an update assessing analgesic interventions was necessary given developments in clinical practice. The American College of Obstetricians and Gynecologists has provided recommendations for postpartum pain

management which are available on their website.

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 analgesics such as paracetamol and NSAIDs as basic 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.

Caesarean section is associated with moderate to severe postoperative pain in a significant proportion of women, which may delay recovery and return to activities of daily living; impair mother-child bonding; impact maternal psychological well-being; and may complicate breastfeeding [1]. Furthermore, inadequate postoperative pain relief may lead to hyperalgesia and persistent postoperative pain [2].

Pain after caesarean section is often undertreated due to unfounded fears that analgesic drugs or interventions might induce maternal and neonatal side effects and because the severity of post-caesarean section pain is often underestimated [3]. Based on a systematic review performed in 2014 [4], the PROSPECT Working Group [5 , 6], which is a collaboration of surgeons and anaesthetists, previously provided recommendations for pain management in women undergoing caesarean section. Recently, several new techniques have been developed to manage pain after caesarean, such as the quadratus lumborum block; slow-release local anaesthetics; and non-pharmacological approaches. Additionally, in the last decade, attention has shifted to reduce opioid use and to implement protocols for enhanced recovery after caesarean section. Therefore, an updated systematic review on analgesic interventions for pain management after elective caesarean section performed using neuraxial anaesthesia was needed. 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 [7 , 8].

The aim of this systematic review was to provide updated recommendations based on recent literature assessing the impact of analgesic and surgical approaches on pain after elective caesarean section performed under neuraxial anaesthesia. Postoperative pain scores were the primary outcome measures. Other recovery outcomes assessed included cumulative opioid consumption and adverse effects. The limitations of the available evidence were also assessed. The ultimate aim was to develop recommendations for pain management after elective caesarean section performed under neuraxial anaesthesia.

The methods of this review adhered to the previously reported PROSPECT methodology [8]. 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 randomised controlled trials, systematic reviews and meta-analyses published between 1 May 2014 and 22 October 2020. The search terms used were: (cesarean section OR cesarean OR cesarean delivery) AND (pain OR postoperative pain OR analgesia OR anesthesia OR anaesthesia 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 peritoneal closure OR skin incision OR skin closure). Only studies in which patients underwent elective caesarean section under neuraxial anaesthesia were included.

Quality assessment, data extraction and data analysis adhered to the PROSPECT methodology [8]. In this study, we defined a change of more than 10/100 mm on the visual analogue scale or numerical rating score as clinically relevant [8]. The effectiveness of each intervention for each

outcome was evaluated qualitatively by assessing the number of studies showing a significant difference between treatment arms. We also evaluated for each study if patients received 'basic' analgesia (i.e. paracetamol and/or NSAIDs) and 'baseline' analgesia (i.e. routine administration of an analgesic additional to the study intervention). We decided not to perform a meta-analysis a priori due to heterogeneity in study design and result reporting, restricting pooled analysis.

Recommendations were made according to PROSPECT methodology [8]. 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. The Obstetric Anaesthetists' Association Executive Committee were consulted on the final PROSPECT recommendations and offered their support.

A total of 145 studies were included, of which 126 were randomised controlled trials and 19 were systematic reviews and meta-analyses (Fig. 1) [9 , 10 , 11 , 12 , 13 , 14 , 15 , 16 , 17 , 18 , 19 , 20 , 21 , 22 , 23 , 24 , 25 , 26 , 27 , 28 , 29 , 30 , 31 , 32 , 33 , 34 , 35 , 36 , 37 , 38 , 39 , 40 , 41 , 42 , 43 , 44 , 45 , 46 , 47 , 48 , 49 , 50 , 51 , 52 , 53 , 54 , 55 , 56 , 57 , 58 , 59 , 60 , 61 , 62 , 63 , 64 , 65 , 66 , 67 , 68 , 69 , 70 , 71 , 72 , 73 , 74 , 75 , 76 , 77 , 78 , 79 , 80 , 81 , 82 , 83 , 84 , 85 , 86 , 87 , 88 , 89 , 90 , 91 , 92 , 93 , 94 , 95 , 96 , 97 , 98 , 99 , 100 , 101 , 102 , 103 , 104 , 105 , 106 , 107 , 108 , 109 , 110 , 111 , 112 , 113 , 114 , 115 , 116 , 117 , 118 , 119 , 120 , 121 , 122 , 123 , 124 , 125 , 126 , 127 , 128 , 129 , 130 , 131 , 132 , 133 , 134 , 135 , 136 , 137 , 138 , 139 , 140 , 141 , 142 , 143 , 144 , 145 , 146 , 147 , 148 , 149 , 150 , 151 , 152 , 153]. The methodological quality assessments of the 126 randomised controlled trials included in the final qualitative analysis are summarised in online Supporting Information Table S1 . The characteristics of the included studies are shown in online Supporting Information Tables S2 and S3 .

Flow diagram of studies included in this systematic review.

When paracetamol was administered pre-operatively rather than at the end of surgery, only minor differences were noted [9]. In one study, rectal paracetamol was shown to be superior to pre-operative oral paracetamol combined with i.v. paracetamol at the end of surgery [10]. In one study, opioid consumption was reduced with i.v. paracetamol compared with placebo but there was no difference in pain scores [11]. In another study, no differences in opioid consumption and pain scores were noted with i.v. paracetamol [12].

A meta-analysis concluded that systemic NSAIDs reduced pain scores, decreased opioid consumption, reduced opioid-related side effects and increased patient satisfaction [13]. A Cochrane review evaluated oral analgesics, comprising primarily but not exclusively NSAIDs, but could not draw any conclusions due to the low quality of studies, small number of included patients and substantial heterogeneity in the studied drugs (paracetamol; celecoxib; ibuprofen; gabapentin; combination) [14]. Inthigood et al. evaluated a single dose of i.v. parecoxib 40 mg and noted better pain scores than with placebo [15]. Three studies compared an NSAID with an opioid and demonstrated equally effective or superior analgesia with NSAIDs [16 , 17 , 18]. The addition of rectal diclofenac to pentazocine was also associated with better analgesia than pentazocine alone [19].

Four randomised controlled trials [20 , 21 , 22 , 23] and a meta-analysis [24] evaluated pre-operative gabapentinoids for analgesia after caesarean section. No significant benefits were reported with gabapentin when added to a multimodal analgesia regimen [20]. The multimodal regimen consisted of intrathecal morphine, rectal and oral paracetamol and i.v. and oral NSAID [20]. Administration of pregabalin combined with intramuscular diclofenac, but without intrathecal morphine, was associated with lower pain scores and reduced opioid requirements [21]. In another study, gabapentin provided superior analgesia compared with intrathecal fentanyl [22]. In the two latter studies, basic analgesia consisted of diclofenac [21 , 22]. In a study conducted on patients

who did not receive any basic analgesia, adding vitamin B complex to gabapentin reduced pain scores and opioid consumption compared with the use of gabapentin alone [23]. A systematic review reported a clinically significant reduction in 24-h pain scores with preoperative gabapentin. Side effects such as sedation and dizziness were reported in several of the included studies [24].

Adding i.v. lidocaine to i.v. patient-controlled analgesia (PCA) with morphine did not improve pain scores or opioid consumption [25]. One randomised controlled trial evaluated the effects of i.v. ketamine on postoperative analgesia [26]. A bolus of i.v. ketamine after delivery of the fetus reduced pain and rescue analgesics in the first 12 h after caesarean section [26]. In the latter study, no basic analgesia or additional baseline analgesia was given [26]. A meta-analysis on the i.v. use of ketamine demonstrated marginal improvements in pain scores and a mild reduction in morphine consumption [27].

Compared with sufentanil PCA alone, the addition of dexmedetomidine to a sufentanil PCA in the postoperative period was associated with lower pain scores, reduced sufentanil consumption, reduced need for rescue analgesia and a higher patient satisfaction. However, the improved pain scores were not clinically relevant [28]. In the latter study, no basic or additional baseline analgesia was given [28].

Four randomised controlled trials evaluated the use of i.v. dexamethasone [29 , 30 , 31 , 32]. Use of i.v. dexamethasone was associated with better pain scores; prolongation of analgesic effect [29]; a reduction in opioid consumption [30]; and a reduced need for postoperative antiemetics [31]. One study reported better analgesia when dexamethasone was administered as wound infiltration as opposed to i.v. administration [32]. Intravenous dexamethasone was not as effective as i.v. tramadol [32].

Several studies compared various systemic opioids (oxycodone; sufentanil; tramadol; dezocine; butorphanol; hydromorphone; tapentadol) [33 , 34 , 35 , 36 , 37 , 38 , 39 , 40]. No individual drug was clearly superior in terms of analgesia or side effect profile compared with any other opioid.

One meta-analysis [41] and three randomised controlled trials [42 , 43 , 44] evaluated the administration of intrathecal morphine. The meta-analysis compared low (50–100 µg) and high (> 100 µg) doses of intrathecal morphine and concluded that high doses increase the duration of analgesia but were more likely to be associated with side effects. Pain scores were similar in both groups [41]. A dose-response study of intrathecal morphine showed that 50 µg doses were as effective as 100 µg and 150 µg, with a similar requirement for rescue opioids. The risk of pruritus was lowest after 50 µg morphine [42]. In patients with an anticipated high pain intensity (such as patients with chronic pelvic pain), pain scores with movement were lower in patients receiving 300 µg vs. those receiving 150 µg intrathecal morphine [43]. In a comparative study, intrathecal morphine provided better analgesia compared with epidural morphine and patient-controlled epidural analgesia of ropivacaine with sufentanil [44]. In two studies, women were offered to choose the analgesic strategy and select either no intrathecal morphine or a low or high dose of intrathecal morphine [45 , 46]. Having a choice did not impact on rescue opioid consumption, but women were very good in predicting their actual opioid needs. Choosing high-dose intrathecal morphine was associated with increased rescue analgesia and more vomiting [45 , 46]. Apart from one study [44], all studies used basic analgesia with NSAIDs [42 , 43 , 46] or a combination of NSAIDs and paracetamol [45]. Intrathecal morphine was similar to intrathecal hydromorphone in a recent trial by Sharpe et al. [47].

Ten trials evaluated the neuraxial administration of α_2 -agonists such as clonidine and dexmedetomidine [48 , 49 , 50 , 51 , 52 , 53 , 54 , 55 , 56 , 57]. A meta-analysis showed that neuraxial clonidine increased the duration and quality of analgesia and reduced morphine consumption [48]. However, more side effects such as hypotension and intraoperative sedation were noted. No improvements in analgesia were reported with intrathecal or i.v. clonidine, whether administered alone [49] or in combination with intrathecal morphine [50]. One study

demonstrated the superiority of intrathecal clonidine to intrathecal fentanyl [51]. Addition of epidural dexmedetomidine to combined spinal-epidural anaesthesia resulted in improved intra-operative and postoperative analgesia and less requirements for opioid rescue [52]. A comparison of intrathecal dexmedetomidine with intrathecal morphine did not demonstrate any significant differences in duration of analgesia, pain scores or need for rescue analgesia. However, both intrathecal morphine and intrathecal dexmedetomidine provided better analgesia when compared with isobaric bupivacaine (53). Administration of intrathecal dexmedetomidine resulted in improved postoperative analgesia when compared with isobaric bupivacaine or ropivacaine alone [54 , 55]. Intrathecal dexmedetomidine combined with intrathecal magnesium sulphate or intrathecal morphine improved analgesia which was of longer duration than analgesia produced by magnesium sulphate alone [56 , 57]. Adding intrathecal fentanyl to bupivacaine improved initial analgesia [58]. However, when morphine is also added to the intrathecal mixture, fentanyl might induce acute opioid tolerance and result in greater opioid consumption [59]. Intrathecal buprenorphine [60] and epidural hydromorphone [61] resulted in improved postoperative analgesia and reduced opioid consumption compared with intrathecal bupivacaine or ropivacaine alone.

A meta-analysis evaluating the effect of neuraxial magnesium on postoperative analgesia demonstrated a longer duration of sensory block, lower pain scores and reduced rescue analgesia requirements than neuraxial mixtures of local anaesthetic without magnesium [62].

The use of intrathecal midazolam was evaluated in several studies [63 , 64]. A comparative study demonstrated that intrathecal magnesium and intrathecal sufentanil were superior to intrathecal midazolam [63]. Intrathecal midazolam prolonged the duration of spinal anaesthesia when compared with placebo [64]. Intrathecal ketamine prolonged analgesia when compared with fentanyl [65 , 66]. A meta-analysis showed that intrathecal neostigmine improved analgesia after caesarean section, although it was associated with an increased risk of nausea and vomiting [67]. A study showed that a faster speed of intrathecal injection of fentanyl and local anaesthetic results in improved postoperative analgesia with a more sustained duration [68].

Intraperitoneal local anaesthetic instillation resulted in lower early pain scores [69], and reduced pain scores at 24 h in a subgroup in which the peritoneum was closed [69]. The use of topical analgesia (e.g. eutectic mixture of local anaesthetic cream) failed to reduce pain scores at 24 and 48 h [70].

Three studies demonstrated that local anaesthetic wound infiltration reduced pain scores and the need for rescue analgesia during the first 24 h after caesarean section [71 , 72 , 73], while one study showed only limited benefits [74]. Apart from one study [72], basic analgesia with ibuprofen and paracetamol was provided. Another two studies which used multimodal analgesia showed improved pain scores, less morphine consumption and higher breastfeeding comfort with continuous wound infusion compared with no infusion [75 , 76]. Local anaesthetic wound infusion resulted in similar analgesic effects as intrathecal morphine [76]. A meta-analysis confirmed that both single-shot local anaesthetic wound infiltration and continuous wound infusion reduce postoperative opioid consumption and mildly improve pain scores [77]. Pain scores were similar whether the catheter was placed preperitoneal or subcutaneously [78]. Adding ketorolac improved analgesia of wound infiltration and reduced opioid consumption [79]. In a recent study, ketorolac added to wound infiltration did not improve analgesia but intrathecal morphine was administered in both groups [80]. Magnesium and dexmedetomidine as adjuvants to wound infiltration reduced pain scores [81 , 82].

A rectus sheath block provides no additional analgesic benefit when added to multimodal analgesia which also includes intrathecal morphine [83]. Adding a field block after caesarean section to intrathecal morphine also did not improve analgesia after caesarean section [84].

There were five studies that compared transversus abdominis plane (TAP) blocks against placebo or no TAP block [85 , 86 , 87 , 88 , 89]. Apart from one study [85], all studies noted that TAP

blocks improved pain relief, increased patient satisfaction and resulted in a reduction of rescue analgesia. A comparison between lateral and posterior approaches concluded that the posterior approach resulted in better pain scores which was only clinically relevant at 12 h postoperatively. This approach also resulted in reduced need for rescue analgesia [90]. Comparison between surgeon-administered and anaesthetist-administered TAP blocks did not show any differences in postoperative analgesia [91].

Several studies evaluated the role of local anaesthetic adjuvants for TAP blocks. Pain scores, opioid consumption and duration of analgesia were significantly improved when dexamethasone was added to local anaesthetic for TAP blocks [92]. Fentanyl added to TAP blocks failed to improve the quality of analgesia [93]. The addition of α_2 -agonists (clonidine or dexmedetomidine) prolonged the duration of analgesia, reduced the need for rescue drugs and improved patient satisfaction [94 , 95 , 96]. However, mild sedation was noted in some patients [94 , 95 , 96].

Several studies compared TAP blocks with alternative regional anaesthesia techniques [97 , 98 , 99 , 100 , 101 , 102 , 103]. In a comparison of TAP blocks with epidural analgesia which included high-dose epidural morphine, improved analgesia with the epidural analgesia was noted [97]. Three studies compared intrathecal morphine with TAP blocks [98 , 99 , 100]. In two of these, there was better analgesia with intrathecal morphine and a reduced requirement for rescue analgesia. However, postoperative mobilisation and return of gastrointestinal function was better with TAP blocks [98 , 99]. The third study could not discriminate between the two techniques in terms of pain relief and other clinical outcomes [100]. Three randomised controlled trials compared TAP blocks with continuous local anaesthetic wound infusion and noted no differences in postoperative analgesia [101 , 102 , 103].

Three meta-analyses confirmed the efficacy of TAP blocks for analgesia after caesarean section but concluded that they do not confer any benefit over intrathecal morphine [104 , 105 , 106]. A combination of ilioinguinal and iliohypogastric nerves block with TAP blocks vs. no blocks resulted in less rescue opioid consumption and lower pain scores [107]. Adding dexmedetomidine to a ropivacaine bilateral ultrasound-guided TAP block resulted in lower postoperative pain scores and less rescue opioid [108]. Quadratus lumborum blocks were evaluated in 11 trials [109 , 110 , 111 , 112 , 113 , 114 , 115 , 116 , 117 , 118 , 119]. Compared with a sham block, quadratus lumborum blocks produced better analgesia. In two trials quadratus lumborum blocks were found to be superior to a TAP blocks [113 , 114 , 118 , 119]. In one study, quadratus lumborum blocks were less effective than a single epidural bolus of local anaesthetic [115]. Adding quadratus lumborum blocks to intrathecal morphine did not improve analgesia [116]. However, in a direct comparison, a quadratus lumborum block was similar to intrathecal morphine [117]. Two recent meta-analyses evaluated TAP blocks, wound infusion and quadratus lumborum blocks with or without intrathecal morphine and concluded that all three regional anaesthetic techniques are superior to no regional technique in the absence of intrathecal morphine [120 , 121]. When intrathecal morphine is administered, adding these techniques confers no further advantages.

Two studies recently evaluated the erector spinae plane block (ESP) compared with TAP block and intrathecal morphine and in both studies the ESP block improved analgesia [122 , 123].

Patient-controlled epidural analgesia added to intrathecal morphine resulted in a further lowering of postoperative pain scores and less need for rescue opioid [124]. Adding fentanyl to patient-controlled epidural analgesia with levobupivacaine did not improve analgesia [125].

Several investigators reported on the beneficial effects of transcutaneous electrical nerve stimulation on pain scores, rescue analgesia use and patient satisfaction [126 , 127]. A study demonstrated that self-administered oral opioid analgesia was as effective as parenteral nurse-administered drugs [128]. A comparison of a fixed time-interval with on-demand oral analgesia concluded that the latter was associated with better pain scores [129]. One study evaluated the use of relaxation sounds intra- or postoperatively and showed improved pain scores [130]. One study evaluated the use of early skin-to-skin contact between mother and baby and

noted no differences in postoperative pain scores [131].

Three studies evaluated the use of elastic abdominal binders after caesarean section [132 , 133 , 134]. In all three, a clinically relevant reduction in pain scores and rescue analgesia was noted [132 , 133 , 134]. Two studies evaluated the application of manual cervical dilation at the end of caesarean section and compared it with no cervical dilation and came to conflicting conclusions [135 , 136]. One study noted improved pain scores until 7 days postoperatively [135] while the other did not report any pain reduction [36]. Preoperative vaginal cleansing resulted in minor but statistically significant reductions in postoperative pain scores [137].

A systematic review [138] confirmed the superiority of the Joel-Cohen (also called modified Misgav-Ladach) incision compared with Pfannenstiel incision in reducing postoperative pain [139]. No differences in pain scores were noted between using a scalpel vs. diathermy for the skin incision [139].

A blunt fascial opening resulted in less postoperative pain [140]. The older technique of extraperitoneal section was associated with better pain scores up to 48 h postoperatively [141]. In one study, the absence of making a bladder flap at opening the uterus resulted in clinically relevant improvements in postoperative pain scores [142]. A comparison between uterine exteriorisation and in situ closure of the uterus showed more postoperative pain with exteriorised uteri [143]. However, one meta-analysis did not show any difference in postoperative pain between the two modalities of uterine closure [144].

A comparison between two techniques of pyramidalis muscle dissection found no differences in postoperative pain [145]. Reduced pain scores when the peritoneum was not closed were reported [146]. One study reported a significant reduction in postoperative pain scores when the rectus muscle was not reapproximated [147]. A Cochrane review noted minimal evidence for reduced pain scores when the peritoneum was not closed after caesarean section [148]. When applying laser irradiation to the caesarean section wound at the end of surgery, less pain during the first 24 h postoperatively was noted [149 , 150]. No differences in pain scores were noted between interrupted and continuous wound suturing [151]. Similarly, two meta-analyses did not show any difference in pain scores whether skin closure was performed with sutures or staples [152 , 153].

The majority of the studies included in this systematic review were determined to be of high quality. The updated literature strengthens the previous PROSPECT recommendations for pain management in patients undergoing elective caesarean section and modifies it in certain aspects. The updated PROSPECT methodology further strengthens the recommendations, because it goes beyond assessment of the available evidence based solely on statistical analysis [8].

Of note, it is essential to highlight that this guideline focuses on elective caesarean section under neuraxial anaesthesia. Importantly, these recommendations should not be applied to other patient populations such as emergency or unplanned caesarean section or surgery performed under general anaesthesia.

The recommended strategies have sufficient procedure-specific evidence and have a positive balance of clinical benefits and risk of side-effects (Table 1). Basic analgesia after caesarean section should always consist of paracetamol and NSAIDs started intraoperatively (after delivery) and continued postoperatively, unless there are contra-indications. Of note, several studies demonstrated equally good pain control with NSAIDs compared with opioids. Regular administration of basic analgesics is important to limit the need for rescue opioid analgesia. Moreover, studies investigating an analgesic strategy to manage pain relief after caesarean section should not omit this basic strategy of analgesia so as to establish the additional value of an investigational approach. In addition to basic analgesics, i.v. dexamethasone demonstrated positive effects on pain scores and opioid consumption. In addition, i.v. dexamethasone provides anti-emetic prophylaxis. Thus, i.v. dexamethasone is recommended. Caution is required in

patients with glucose intolerance.

Overall recommendations for pain management in patients undergoing elective caesarean section.

Intrathecal long-acting opioid (e.g. morphine 50–100 µg or diamorphine up to 300 µg) (Grade A). Epidural morphine 2–3 mg or diamorphine up to 2–3 mg may be used as an alternative, for example, when an epidural catheter is used as part of a combined spinal-epidural technique (Grade A)

Intravenous paracetamol if not administered pre-operatively (Grade A)

Intravenous non-steroidal anti-inflammatory drugs (Grade A)

If intrathecal morphine not used, local anaesthetic wound infiltration (single-shot) or continuous wound infusion and/or regional analgesia techniques (fascial plane blocks such as transversus abdominis plane blocks and quadratus lumborum blocks) (Grade A)

Oral or intravenous paracetamol (Grade A)

Oral or intravenous non-steroidal anti-inflammatory drugs (Grade A)

Opioid for rescue or when other recommended strategies are not possible (e.g. contraindications to regional anaesthesia) (Grade D)

Analgesic adjuncts include transcutaneous electrical nerve stimulation (Grade A)

John Wiley & Sons, Ltd Intrathecal morphine at doses of 100 µg or lower is recommended. Doses lower than 100 µg result in adequate analgesia with a reduced incidence of side-effects. Recently, Sharawi et al. confirmed the safety of intrathecal morphine when used in patients undergoing caesarean section [154]. Importantly, basic analgesics (i.e. paracetamol and NSAIDs) and i.v. dexamethasone should be used with intrathecal morphine. Of note, the National Institute of Health and Care Excellence (NICE) guidelines in the UK recommend intrathecal diamorphine as an alternative to intrathecal morphine [155]. Intrathecal diamorphine 300 µg is recommended. When spinal anaesthesia is not possible or when an epidural catheter is in situ, epidural morphine or diamorphine both in doses of 2–3 mg can be used.

Various local anaesthetic techniques such as TAP blocks, quadratus lumborum blocks and local anaesthetic wound infiltration are effective in reducing pain scores and opioid requirements. Given that the potential side-effects of these regional analgesic techniques are limited, they are recommended. However, the additional value of any of these techniques when combined with intrathecal morphine appears to be minimal. Therefore, these blocks may be administered if intrathecal morphine is not used.

Surgical techniques that have been shown to be beneficial and are therefore recommended include Joel-Cohen incision and avoidance of peritoneum closure. Using abdominal binders postoperatively is recommended with sufficient procedure-specific evidence being identified. Analgesic adjuncts such as listening to music via headphones and use of transcutaneous electrical nerve stimulation may be associated with improved pain relief and are recommended when available.

Although pre-operative gabapentinoids were recommended previously, they are no longer recommended despite positive studies of their benefits due to concerns about side-effects such as sedation and respiratory depression [156]. Furthermore, it is not clear if gabapentinoids add to our current recommendations of basic analgesia, i.v. dexamethasone and regional analgesia.

Several intraoperative interventions are not recommended due to inconsistent or limited or lack of procedure-specific evidence and/or concerns of side effects (Table 2). For example, intraoperative dexmedetomidine infusion has been shown to provide improved postoperative pain relief; however, it is not recommended because its benefits on top of basic analgesia remain unknown, and due to concerns of side effects including hypotension and bradycardia which can be prolonged and might impede ambulation [157]. Similarly, although, a subanaesthetic dose of i.v. ketamine has demonstrated positive effects on postoperative pain scores [158], it is not recommended because its benefits over basic analgesia are unknown, and concerns of side effects such as hallucinations that might impair the recollection of the birth experience and mother-child bonding [158 , 159].

Analgesic interventions that are not recommended for pain management in patients undergoing elective caesarean section.

John Wiley & Sons, Ltd Intrathecal or epidural administration of buprenorphine, hydromorphone, midazolam, α_2 -adrenergic agonists, neostigmine and ketamine has been reported to prolong the analgesic duration of morphine. However, they cannot be recommended due to inconsistent procedure-specific evidence and due to the potential side effects such as hypotension or sedation. Additionally, in most studies, hypotension occurs as frequently as sedation. Peritoneal instillation of local anaesthetics cannot be recommended due to a lack of procedure-specific evidence. Similarly, topical local anaesthetic cream application is not recommended due to a lack of procedure-specific evidence.

The limitations of this review are related to those of the included studies. There was considerable heterogeneity between studies with regard to dosing regimens and route of administration as well as the timing of pain assessments. The small size of most studies makes it impossible to draw conclusions about the safety profile of an individual intervention. In the majority of included studies, the analgesic intervention was not evaluated against an optimised multimodal analgesic regimen. Moreover, measuring just pain scores and/or opioid consumption is not sufficient and more comprehensive, patient-centred tools to assess pain relief and functionality would better reflect day-to-day clinical practice but are unfortunately poorly reported in the literature. Also, because most studies include healthy, full-term parturients, our recommendations may not be applicable to parturients with coexisting medical conditions such as morbid obesity, chronic pain as well as preterm delivery. Furthermore, the PROSPECT methodology uses a minimal clinically important difference in pain scores of 1/10. However, this difference has never been validated in obstetric patients.

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, hospital stay and the occurrence of chronic pain or chronic opioid consumption. Furthermore, it is necessary to examine the influence of analgesic interventions on patient-reported outcomes such as mother-child bonding, breast feeding ability, time to ambulation and return to activities of daily living. Validated scoring tools such as the quality of recovery¹¹ are useful metrics that should be considered.

In summary, this review has identified an analgesic regimen that can be used for optimal pain management after elective caesarean section performed under neuraxial anaesthesia. A combination of basic analgesics such as paracetamol; NSAIDs or cyclooxygenase-2-selective inhibitors; and i.v. dexamethasone, along with a local/regional analgesic techniques (e.g. intrathecal morphine 50–100 μ g or diamorphine 300 μ g); local anaesthetic infiltration with or without a field blocks such as ilioinguinal and iliohypogastric nerves blocks or fascial plane blocks (e.g. TAP, quadratus lumborum or ESP blocks) are recommended. However, the benefits of local and regional analgesic techniques are not apparent with the use of intrathecal morphine or diamorphine. Analgesic adjuncts such as listening to music via headphones and transcutaneous electrical nerve stimulation may be used when available. Several aspects of the surgical technique clearly yield positive analgesic effects after caesarean section including the Joel-Cohen incision, non-closure

of the peritoneum and the use of abdominal binders. The PROSPECT recommendation for postoperative analgesia after caesarean section has established a multimodal pre-, intra- and postoperative analgesic strategy which combined with certain surgical approaches and adjuvant techniques may provide excellent analgesia.

Table S1. Quality assessment and level of evidence assigned to the randomised trials included in the review for analgesia after caesarean section.

Table S2. Summary of key results from studies evaluating systemic analgesics, analgesics adjuncts, regional anaesthesia and surgical procedures used to support the recommended interventions in patients after caesarean section.

Table S3. Summary of key results from studies evaluating systemic analgesics, analgesics adjuncts, regional anaesthesia and surgical procedures used to support the interventions that are not recommended in patients undergoing caesarean section.

This PROSPECT recommendation is supported by the Obstetric Anaesthetists' Association. PROSPECT is supported by an unrestricted grant from the European Society of Regional Anaesthesia and Pain Therapy. In the past, PROSPECT has received unrestricted grants from Pfizer Inc. New York, NY, USA and Grunenthal, Aachen, Germany. GJ 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. EPZ has received honoraria from Mundipharma, Grunenthal, MSD, Janssen-Cilag GmbH, Fresenius Kabi and AcelRx. No other external funding or competing interests declared.

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