Intrathecal morphine does not prevent chronic postsurgical pain after elective Caesarean delivery: a randomised controlled trial

Subedi, A.; Schyns-van den Berg, A.M.J.V.; Thapa, P.; Limbu, P.M.; Trikhatri, Y.; Poudel, A.; ... ; Bhandari, S.

BJA

British Journal of Anaesthesia, 128 (4): 700–707 (2022)

doi: 10.1016/j.bja.2021.11.036
Advance Access Publication Date: 26 January 2022
Obstetric Anaesthesia

OBSTETRIC ANAESTHESIA

Intrathecal morphine does not prevent chronic postsurgical pain after elective Caesarean delivery: a randomised controlled trial

Asish Subedi[1,*], Alexandra M. J. V. Schyns-van den Berg[2,3], Parineeta Thapa[1], Prakash M. Limbu[1], Yojan Trikhatri[1], Anjali Poudel[4], Yogesh Dhakal[1] and Sabin Bhandari[5]

[1]BP Koirala Institute of Health Sciences, Dharan, Nepal, [2]Albert Schweitzer Hospital, Dordrecht, the Netherlands, [3]Leiden University Medical Centre, Leiden, the Netherlands, [4]Indira Gandhi Memorial Hospital, Male, Maldives and [5]Tribhuvan University Teaching Hospital, Kathmandu, Nepal

*Corresponding author. E-mails: asish_subedi@alumni.harvard.edu, asishsubedi19@gmail.com

Abstract

Background: Morphine is frequently added to spinal anaesthesia for Caesarean delivery. We aimed to determine whether intrathecal morphine for spinal anaesthesia decreases the risk of chronic postsurgical pain (CPSP).
Methods: In this randomised, double-blind, placebo-controlled trial, 290 healthy parturients undergoing elective Caesarean delivery were randomly assigned in a 1:1 ratio to receive either intrathecal morphine 100 μg (n=145) or normal saline (control; n=145) as a part of spinal anaesthesia. Anaesthetic care and postoperative pain management were standardised in all patients. The primary outcome was the incidence of CPSP at 3 months. Secondary outcomes included CPSP at 6 months, pain severity, and pain interference, measured by the Brief Pain Inventory questionnaire using an 11-point numeric rating scale, at 3 and 6 months after the surgery.
Results: Two hundred and seventy-six patients completed the 3-month follow-up, 139 in the morphine group and 137 in the placebo group. The incidences of CPSP at 3 months were 19% (27 of 139) in the morphine group and 18% (25 of 137) in the placebo group (odds ratio, 1.08; 95% confidence interval, 0.59–1.97; P=0.803). At 6 months, CPSP was present in 23 of 139 (16%) morphine group patients compared with 19 of 137 (14%) in the placebo group (odds ratio, 1.23; 95% confidence interval, 0.63–2.38; P=0.536). Brief Pain Inventory questionnaire scores for pain severity and pain interference at 3 and 6 months were similar between groups.
Conclusions: Administration of morphine 100 μg as a component of spinal anaesthesia for elective Caesarean delivery failed to reduce the incidence of chronic pain at 3 and 6 months after surgery.
Clinical trial registration: NCT03451695.

Keywords: Brief Pain Inventory; Caesarean delivery; chronic postsurgical pain; morphine; spinal anaesthesia

Editor's key points

- Caesarean delivery is one of the most commonly performed surgeries worldwide, and over 10% of parturients report persistent pain after cesarean delivery.
- Current guidelines recommend the use of intrathecal morphine combined to spinal anaesthesia to reduce acute pain, but it is unclear whether it may also impact the development of chronic post surgical pain.

Received: 27 August 2021; **Accepted:** 10 November 2021

- In this randomised double blind placebo controlled trial conducted in 290 healthy parturients in Nepal undergoing Caesarean delivery, administration of a single dose of intrathecal morphine (as a component of spinal anesthesia) does not reduce the incidence, severity or functional impact of chronic pain at 3 and 6 months compared to saline, although alleviating acute postoperative pain.
- Effective opioid-induced analgesia does not necessarily have an impact on the further development of persistent pain after Caesarean delivery.

The incidence of chronic postsurgical pain (CPSP) after Caesarean delivery is reported to be in the range between 7 and 30%, reflecting it to be a significant clinical problem.[1] Studies related to prevention of progression of acute post-Caesarean delivery pain to its chronicity are sparse. Severe acute postoperative pain has been consistently linked with chronic post-Caesarean delivery pain.[1] Therefore, effective analgesia in the perioperative period may mitigate the development of persistent pain.

Current guidelines on analgesia recommend the inclusion of long-acting intrathecal (i.t.) opioids to spinal anaesthesia for acute post-Caesarean delivery pain relief.[2] Despite its frequent use, randomised clinical trials related to intrathecal morphine use and its association with chronic pain are lacking. A recent prospective observational study revealed a significant reduction in chronic pain after Caesarean delivery when morphine was used as an adjuvant to spinal anaesthesia.[3] The primary objective of our trial was to compare the effect of morphine with placebo, added to spinal anaesthesia, on the development of chronic pain, 3 months after elective Caesarean delivery. Our secondary objective was to determine the incidence of chronic pain after 6 months, and to assess pain severity and interference scores using the short form Brief Pain Inventory (BPI) at 3 months and 6 months after Caesarean delivery between the morphine and placebo group. We hypothesised that spinal morphine would reduce the incidence of persistent pain after Caesarean delivery.

Methods

This prospective, randomised, double-blind trial was conducted at BP Koirala Institute of Health Sciences (BPKIHS) between April 2018 and March 2021. The study protocol was approved by the institutional review committee (BPKIHS; IRC number: IRC/1183/017). The trial was registered before patient enrolment at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03451695; Principal Investigator: AS; date of registration: March 2, 2018). All participants provided written informed consent, and the trial was conducted in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines.

We enrolled full-term singleton parturients with American Society of Anesthesiologists (ASA) physical status 2 undergoing planned Caesarean delivery under spinal anaesthesia. Exclusion criteria were age <18 yr, contraindication to spinal anaesthesia, preeclampsia, height <150 cm, ASA physical status >2, BMI >40 kg m^{-2}, allergy to any drug used in the study, recent opioid exposure, substance abuse, significant cardiovascular, renal, or hepatic disease, and known fetal abnormalities. Consent for the participation in the study was obtained during pre-anaesthetic visits in the evening before surgery. During this visit, patient baseline characteristics (maternal age, height, weight, BMI, gestational age, socioeconomic background, previous Caesarean delivery, pre-existing chronic pain) were documented. The Kuppuswamy scale adapted for Nepali population was used for assessing socioeconomic status and the scoring was based on education, occupation, and total monthly family income (26–29: upper class, 16–25: upper middle class, 11–15: lower middle, 5–10: upper lower, <5: lower class).[4] Also, preoperative anxiety level (assessed with hospital anxiety and depression scale),[5] pain catastrophising (assessed with pain catastrophising scale),[6,7] and preoperative pain sensitivity (assessed with pain pressure threshold and tolerance using a handheld pressure algometer; details provided in the Supplementary Appendix)[8] were recorded. The investigator also educated the patients regarding the use of numeric rating scale (NRS) scores for postoperative pain and satisfaction.

Eligible consented patients were randomly assigned in a 1:1 ratio to one of the two groups (morphine and placebo groups). We randomised participants using the sequentially numbered, opaque sealed envelopes (SNOSE) technique. A randomisation list was generated in a variable block size of 4/6/8 using the online software (www.sealedenvelope.org) by the anaesthesia clerk. To ensure allocation concealment, the same anaesthesia clerk (SA) prepared the randomly generated number for each patient in an opaque envelope, numbered each envelope sequentially, and sealed it. On the day of surgery, SA handed the envelope to an anaesthesia assistant not involved in the trial. The participants, care providers, and investigators were unaware of the trial-group assignments.

On arrival to the operating room, standard monitoring (noninvasive BP, ECG, and pulse oximetry) was applied. Before administration of spinal anaesthesia, the anaesthesia assistant opened the envelope and prepared the study drug solution accordingly. The anaesthesiologist blinded to the group assignment administered spinal anaesthesia in the lateral position at the L3–L4 or L4–L5 interspace using a spinal needle. The morphine group received i.t. hyperbaric bupivacaine 11 mg (2.2 ml 0.5%), fentanyl 10 μg (0.2 ml), and preservative-free morphine 100 μg (0.1 ml). The placebo group received hyperbaric bupivacaine 11 mg (2.2 ml 0.5%), fentanyl 10 μg (0.2 ml), and normal saline (0.1 ml). A co-loading with i.v. Ringer's lactate solution, 10 ml kg^{-1} was initiated immediately after spinal injection. Patients were positioned supine with a left lateral tilt. Surgery was started once the sensory level tested with pinprick reached T6 or higher. All patients received i.v. ondansetron 4 mg. Hypotension was managed with either phenylephrine or ephedrine at the discretion of the anaesthesiologist. Standard surgical procedures for Caesarean delivery were followed that included Pfannenstiel incision and leaving the peritoneum unsutured at the time of closure. The paediatrician recorded the Apgar score at 1 and 5 min after delivery of the baby.

At the end of surgery, the obstetrician injected bupivacaine 0.25% s.c. in the surgical wound (15 ml in each of the upper and lower sides). Also, ketorolac 30 mg i.v., every 8 h and paracetamol 1 g i.v., every 6 h were administered. After 24 h, they received oral aceclofenac 100 mg every 12 h, and paracetamol 1 g every 6 h. Pain during the first 48 h was treated with i.v. morphine 2 mg every 5 min, keeping the NRS score $\leq$3. In the PACU, patients were observed for approximately 2 h and subsequently transferred to the postnatal unit. Postoperative pain severity was assessed using an 11-point NRS (0=no pain and 10=the worst possible pain) at 2, 6, 12, 24, and 48 h after CS. Patients were asked to rate their pain scores both at rest and

movement. The area of hyperalgesia around the surgical incision was assessed at 48 h postoperatively using a 256-mN von Frey filament (Bioseb; In Vivo Research Instruments, Vitrolles, France). The test was started along four points horizontally and perpendicularly around the surgical wound. It was initiated at a 5 cm point away from the wound and moving in the direction of wound at 5 mm intervals until the patient reported a painful, sore, or sharp feeling. If there was no change in sensation, the test was stopped at 5 mm to the incision. The measurements were registered to calculate the total area of hyperalgesia (in cm^2) as described previously.[9,10] At 48 h, patient satisfaction from postoperative analgesia was assessed using a 5-point scale (1=highly satisfied, 2=satisfied, 3=neutral, 4=not satisfied, and 5=strongly dissatisfied). After discharge from hospital (at 48 h), oral aceclofenac (100 mg) twice daily and paracetamol 1 g, four times per day were prescribed for 3 days. For breakthrough pain during this period patients were asked to take tramadol 50 mg orally as required. At 8 weeks postpartum, patients were assessed for depression using the Edinburgh postnatal depression scale (EPDS).[11]

For assessment of CPSP, patients were contacted by telephone by one of the blinded investigators (YT) at 3 and 6 months after the surgery. CPSP was defined as pain that developed after Caesarean delivery and lasted for at least 3 months after surgery, with the pain being different from other pre-existing pain conditions before surgery.[12] The patients who reported CPSP were asked to answer the short form BPI questionnaire, which contains four questions on pain severity and seven questions on pain interference.[13,14] Pain was rated on a verbal NRS (0–10), with 0=‘no pain’ or ‘no interference’ and 10=‘worst possible pain’ or ‘complete interference’. Participants rated their worst, least, and average pain during the past 24 h and their pain at the time of interview. Participants were also asked to rate the level that pain interferes with daily activities on seven aspects of life (general activity, mood, walking, work, relationship with others, sleep, and enjoyment of life). The primary outcome was the frequency of CPSP at 3 months after surgery. Secondary outcomes were CPSP at 6 months, and BPI scores at 3 and 6 months after surgery.

Sample size and statistical methods

A previous prospective observational study reported the incidence of persistent pain at 3 months after Caesarean delivery to be 46% in those who did not receive i.t. morphine and 28% in those who received i.t. morphine.[3] To detect this difference, with 80% power, at a two-sided significance level of 0.05, we estimated a sample of 123 subjects in each group (Stata version 15, StataCorp, College Station, TX, USA). To account for 15% loss to follow-up, we recruited and randomised a total of 290 patients.

Normality of the data was assessed using a histogram visually and verified using the Shapiro–Wilk test. The Student’s unpaired *t*-test was used for comparing normally distributed data between groups, and the Mann–Whitney rank sum test for non-normally distributed data. Proportions between groups were analysed using the χ^2 test or Fisher exact test, as appropriate. Treatment effects on the incidences of

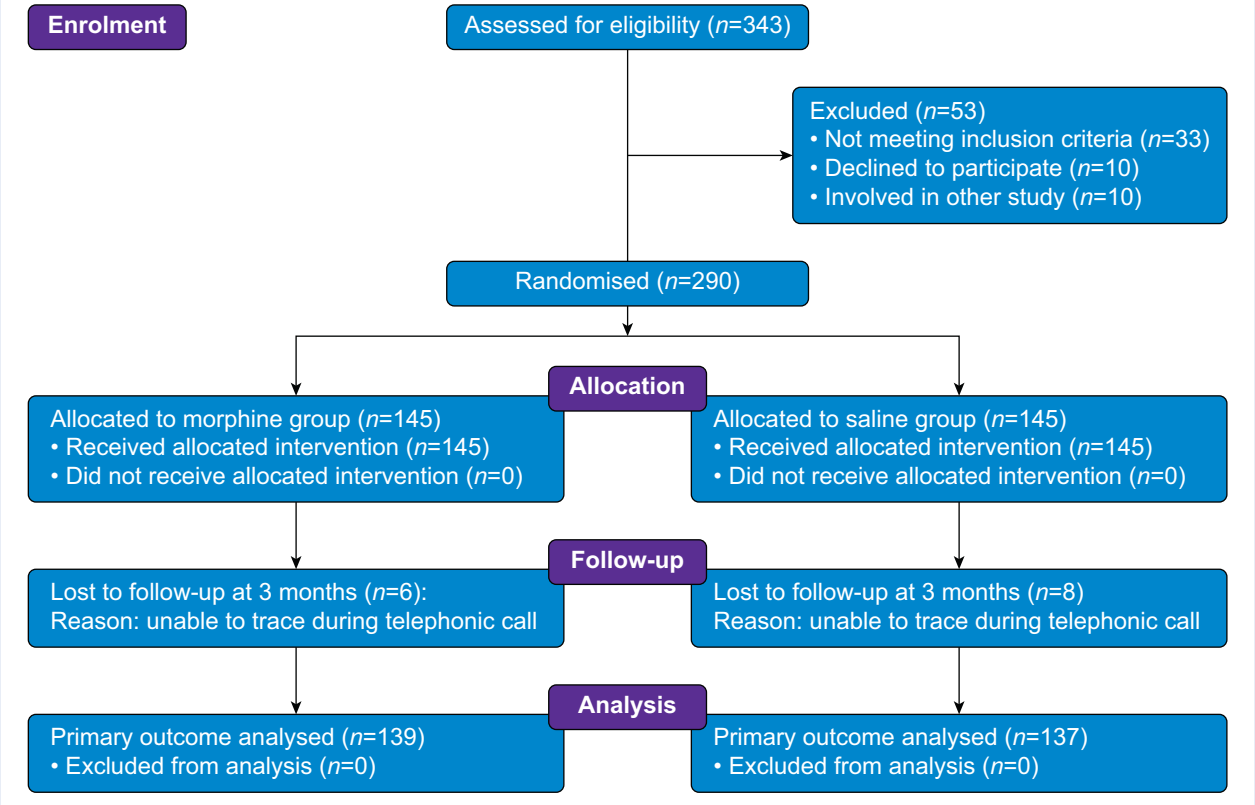

Fig 1. Consolidated Standards of Reporting Trials flow diagram of the study.

Table 1 Baseline patient characteristics and preoperative data. Values are expressed as mean (standard deviation), number (%), or median (inter-quartile range). HADS, Hospital Anxiety and Depression Scale.

Variables	Morphine group n=139	Saline group n=137	P-value
Age (yr)	28.29 (4.88)	28.16 (4.74)	0.816
BMI (kg m^{-2})	27.41 (3.66)	27.46 (3.69)	0.915
Gestational age (weeks)	38.81 (1.26)	38.71 (1.16)	0.505
Ethnicity			0.826
Tibeto-Mongolian	54 (39)	55 (40)	
Indo-Aryan	85 (61)	82 (60)	
Previous Caesarean delivery	94 (68)	91 (66)	0.832
Pre-existing chronic pain	4 (2)	2 (1)	0.684
Socioeconomic status			0.498
Upper class	6 (4)	12 (9)	
Upper middle class	68 (49)	63 (46)	
Lower middle class	41 (30)	41 (30)	
Upper lower class	24 (17)	21 (15)	
HADS (0–21)			
Anxiety	4 (3–6)	4 (3–6)	0.394
Depression	3 (2–4)	3 (2–5)	0.406
Pain catastrophising scores (0–52)	8 (5–13)	8 (6–12)	0.976
Pain pressure threshold (kg)	4.37 (1.26)	4.32 (1.28)	0.766
Pain pressure tolerance (kg)	6.74 (1.53)	6.62 (1.36)	0.517

Table 2 Postoperative data. Values are expressed as median (inter-quartile range), mean (standard deviation), number (%). EPDS, Edinburgh postnatal depression scale; NRS, numeric rating pain scale scores. *Summary statistics of pain scores are reported as mean (standard deviation) of time-weighted average pain during the first 48 h.

	Morphine group n=139	Saline group n=137	P-value
Duration of surgery (min)	60 (45–60)	55 (45–60)	0.123
Pain at rest, up to 48 h*	2.26 (0.72)	2.60 (0.82)	<0.001
Pain during movement, up to 48 h*	3.24 (0.77)	3.63 (0.81)	<0.001
I.V. morphine used up to 48 h (mg)	6 (4–8)	8 (6–10)	<0.001
Severe pain up to 24 h (NRS ≥7)	6 (4)	14 (10)	0.059
Severe pain up to 48 h (NRS ≥7)	10 (7)	19 (14)	0.071
Secondary hyperalgesia at 48 h (cm^2)	51 (17–76)	39 (19–80)	0.819
Satisfaction, postoperative analgesia			0.400
Highly satisfied	20 (14)	16 (12)	
Satisfied	85 (61)	73 (53)	
Neutral	27 (19)	36 (26)	
Dissatisfied	5 (4)	9 (7)	
Strongly dissatisfied	2 (1)	3 (2)	
EPDS scores ≥11 (8 weeks)	10 (7)	14 (10)	0.373

CPSP were presented as odds ratio, with a 95% confidence interval (CI). For NRS pain scores over a period of 48 h, we calculated the area under the curve (AUC) using the trapezoidal rule. Next, time-weighted average pain during the first 48 h for each patient was obtained dividing the AUC by the time interval between the first (2 h) and the last (48 h) NRS measurements. Statistical analysis was performed using Stata version 15. A 2-sided P-value <0.05 was considered as statistically significant.

Results

Of 290 patients randomised, 145 received i.t. morphine and 145 did not receive i.t. morphine; 14 patients were lost to follow-up (Fig. 1). The complete case analysis for primary outcome involved 276 patients (139 in the morphine group and 137 in the control group). We carried out a complete case analysis because we assumed that the data for the primary outcome were missing completely at random (unable to trace during telephone call). Patient characteristics, preoperative anxiety level and pain catastrophising scores, pain pressure threshold, and pain pressure tolerance are shown in Table 1. Immediate postoperative outcomes and outcomes after hospital discharge (EPDS scores) are shown in Table 2. The pain scores (on rest and during movement) at different time points up to 48 h are shown in Supplementary Table S1 in the Supplementary Appendix. The time-weighted average postoperative pain scores and total morphine requirements up to 48 h were significantly higher in the saline group than the morphine group (Table 2). However, no difference was detected in terms of acute severe postoperative pain.

Overall, 52 (18%) patients reported CPSP at 3 months. CPSP at 3 months was diagnosed in 27 (19%) patients assigned to receive i.t. morphine, compared with 25 (18%) patients in the saline group (odds ratio in the morphine group, 1.08; 95% CI, 0.59–1.97; P=0.803) (Fig. 2). The incidence of CPSP at 6 months

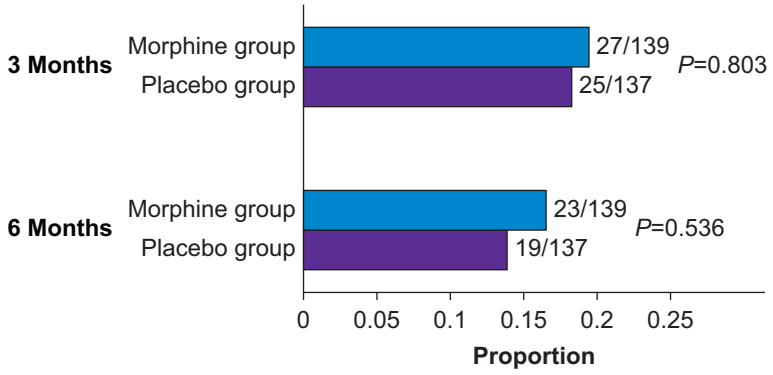

Fig 2. Incidence of chronic postsurgical pain at 3 and 6 months after surgery.

Table 3 Description of chronic postsurgical pain at 3 and 6 months after surgery. Values are expressed as mean (standard deviation). BPI, brief pain inventory. *BPI pain severity and pain interference assessed by numeric rating scale scores (0–10). †Analysed by Mann–Whitney U-test.

	3 Months			6 Months		
	Morphine group n=27	Saline group n=25	P-value	Morphine group n=23	Saline group n=19	P-value
BPI pain severity*†						
Worst pain in past 24 h	3.51 (1.15)	3.76 (0.83)	0.296	2 (0.67)	2.36 (0.76)	0.116
Least pain in past 24 h	1.85 (0.71)	2.04 (0.61)	0.297	1.60 (0.72)	1.57 (0.90)	0.882
Average pain in past 24 h	2.22 (0.84)	2.52 (0.87)	0.222	1.91 (0.59)	2.21 (0.71)	0.140
Current pain	2.18 (0.87)	2.36 (0.70)	0.280	1.60 (0.89)	1.68 (0.88)	0.760
BPI pain interference*†						
General activities	2.14 (0.86)	2.56 (0.96)	0.186	1.56 (0.84)	1.78 (0.63)	0.457
Mood	1.33 (1.03)	1.92 (1.55)	0.196	1.65 (0.64)	1.89 (0.73)	0.209
Walking ability	1.18 (1.07)	1.84 (1.57)	0.128	1.34 (0.77)	1.57 (1.07)	0.727
Normal work	1.25 (1.05)	1.96 (1.56)	0.101	1.21 (0.90)	1.47 (1.12)	0.436
Relations with other people	0.96 (0.93)	1.60 (1.38)	0.086	1.43 (0.66)	1.78 (0.91)	0.133
Sleep	1.33 (1.17)	1.76 (1.58)	0.393	1.47 (0.59)	1.68 (1.00)	0.338
Enjoyment of life	1.03 (0.97)	1.56 (1.32)	0.151	1.39 (0.65)	1.47 (1.02)	0.745

did not differ significantly between the two groups: morphine 23 of 139 (17%) *vs* saline 19 of 137 (14%), odds ratio in the morphine group 1.23 (95% CI, 0.63–2.38; P=0.536). We detected no significant differences between the two groups for the BPI pain severity and pain interference scores at 3 and 6 months after surgery (Table 3).

Discussion

In this clinical trial, we were unable to demonstrate a significant difference in the incidence of chronic pain after planned Caesarean delivery at 3 and 6 months between the parturients who received i.t. morphine and the parturients who did not receive i.t. morphine for spinal anaesthesia. Furthermore, between the morphine and the placebo groups, there was no significant difference in the BPI scores for pain severity and pain interference during the 3- and 6-month follow-up in patients who reported CPSP.

Caesarean delivery is one of the commonly performed surgeries worldwide, and >10% of parturients report persistent pain after wards.[1,15] CPSP after surgery is a significant clinical problem, as it adversely impacts the parturients quality of life and may compromise infant care. Reports have shown a consistent association between severe acute postoperative pain and CPSP after Caesarean delivery[1] Therefore, application of a multimodal analgesic regimen that includes long-acting neuraxial opioids is beneficial. Moriyama and colleagues[3] reported in their observational study that i.t. morphine 100 μg decreased the incidence of a CPSP after Caesarean delivery (adjusted odds ratio 0.424; 95% CI 0.202–0.889, P=0.023). Surprisingly, in the study by Moriyama and colleagues,[3] there was no significant difference in the acute postoperative pain and the reasons as to how i.t. morphine decreased the incidence of CPSP was also not mentioned.

Intrathecal morphine acts in various levels of pain pathways (spinal and supraspinal) and provides prolonged duration of analgesia (up to 24 h).[16] Because i.t. morphine is effective in reducing the intensity of early postoperative pain, we hypothesised that it may indirectly decrease the incidence of CPSP. This assumption is also supported by a meta-analysis which showed a reduction in CPSP with the use of neuraxial anaesthesia.[17] However, our clinical trial failed to demonstrate

the protective role of i.t. morphine. One reason could be because we had used i.t. fentanyl and multimodal analgesia (including local anaesthetic infiltration at the incision site) in both groups and, therefore, it did offer some protection in the placebo group. The other reason is that single shot i.t. morphine may not have any beneficial role in the late postoperative period. Because the transition from acute to CPSP is complex in nature, continuation of preventive modalities beyond the early postoperative period may be beneficial in high-risk groups. However, such modalities in the obstetric population are practically challenging because of safety, ethical, and feasibility issues.

The mechanism of CPSP is partly explained by central sensitisation, a phenomenon of neuronal hyperactivity and hyperexcitability in the spinal cord and brain that occurs after surgical insult.[18] Animal studies have shown that i.t. morphine has inhibitory effects on nociception in the spinal dorsal horn.[16,19,20] However, whether this analgesic mechanism of i.t. morphine is sufficient to attenuate central sensitisation is not fully elucidated. In fact, intrathecally administered morphine has shown conflicting results in a chronic pain model.[21] For example, in a model of sustained nociception, it produced analgesic effects,[22,23] whereas others reported that it is less effective in animal models of chronic neuropathic pain.[24,25] Notably, contradictory findings in the previous studies may be attributable to differences in the timing of its administration.

Secondary mechanical hyperalgesia (i.e. increase pain sensitivity outside the area of the wound) is the consequence of central sensitisation,[26] and it may be a prognostic marker for the subsequent development of persistent pain.[27–29] The modulatory effects of i.t. morphine on nociception-induced hyperalgesia in animal models of postoperative pain remains unclear.[30,31] Intrathecal morphine (both pre-incisional and post-incisional), in comparison with the saline, did not result in a significant reduction in mechanical hyperalgesia beyond 5 h of incisional pain in a rat model.[30] In healthy volunteers, administration of systemic morphine in experimentally induced secondary hyperalgesia showed inconsistent results,[32–34] whereas clinical studies on i.t. morphine and secondary hyperalgesia are lacking.

Although it was statistically insignificant, we observed an increased area of secondary hyperalgesia in the i.t. morphine group as compared with those who did not receive i.t. morphine. Whether this paradoxical finding is attributed to opioid-induced hyperalgesia (OIH) is a matter of debate. In laboratory and clinical studies, chronic administration of spinal morphine is linked to the genesis of OIH, suggesting that OIH is dose- and time-dependent.[35] Interestingly, even acute exposure to opioid can produce OIH. A single dose of spinal fentanyl for Caesarean delivery increased postoperative i.v. morphine requirements.[36] However, because of the limited data, it is inconclusive that a single dose of spinal morphine contributes to the development of OIH. Moreover, as a result of the poorly understood mechanism of OIH and lack of standardised pain sensitivity tools to diagnose OIH, it is difficult to establish a causal relationship between perioperative i.t. opioid exposure and the development of OIH. Nevertheless, this is an important area to explore in future studies because of the linkage between postoperative OIH and CPSP.[37]

In our study, we assessed pain interference on quality of life using the BPI questionnaire in patients who reported CPSP at 3 and 6 months after Caesarean delivery. There was no significant difference in BPI scores between patients who received i.t. morphine and patients who did not receive i.t. morphine. Similar to our findings, Foadi and colleagues[38] demonstrated that intrathecally administered morphine was not associated with improved quality of life or physical function at 6 months after knee or hip surgery. This reflects that a single dose of i.t. morphine may not produce long-term beneficial effects despite better perioperative pain control.

There are certain limitations to our study. First, the concept of 'one size does not fit all' is growing and the experts have proposed that the effective preventive strategies should be tested in the high-risk group. Unfortunately, a risk prediction tool or scoring system for CPSP after Caesarean delivery is lacking. Development of such validated tools or scoring systems in the future will help to stratify the vulnerable group preoperatively. Second, this trial was carried out in a single centre situated in Nepal. Third, most reviews/studies on psychosocial risk factors for CPSP have focussed on high-income countries.[39] There may be differences in the psychological and socio-environmental factors between the Nepali and Western population, and therefore, the findings of this study may limit generalisability. Fourth, we used telephonic interview to assess CPSP and BPI questionnaire because we felt that many patients might not visit the hospital after discharge because of financial and logistic reasons. Finally, the follow-up period after surgery was limited to 6 months only.

In conclusion, our study failed to demonstrate any significant advantage of i.t. morphine 100 μg over placebo on the incidence of CPSP at 3 and 6 months after elective Caesarean delivery. Also, we found no evidence that the use of i.t. morphine affected the pain severity and pain interference at 3 and 6 months after surgery.

Authors' contributions

Study design: AS, ASvdB
Study conduct/data collection: AS, PT, PML, YT, AP, YD, SB.
Data analysis/data interpretation: AS, ASvdB
Writing of the manuscript: AS.
Critical revision of the manuscript: AS/ASvdB
Final approval of the manuscript: all authors.

Declarations of interest

The authors declare that they have no conflict of interest.

Funding

International research grant from the Obstetric Anaesthetists' Association (OAA), United Kingdom.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.11.036.

References

1. Komatsu R, Ando K, Flood PD. Factors associated with persistent pain after childbirth: a narrative review. *Br J Anaesth* 2020; **124**: e117–30
2. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society for

Obstetric Anesthesia and Perinatology. *Anesthesiology* 2016; **124**: 270–300
3. Moriyama K, Ohashi Y, Motoyasu A, Ando T, Moriyama K, Yorozu T. Intrathecal administration of morphine decreases persistent pain after cesarean section: a prospective observational study. *PLos One* 2016; **11**: e0155114
4. Ghosh A, Ghosh T. Modification of Kuppuswamys socio-economic status scale in context to Nepal. *Indian Pediatr* 2009; **46**: 1104–5
5. Risal A, Manandhar K, Linde M, Koju R, Steiner TJ, Holen A. Reliability and validity of a Nepali-language version of the hospital anxiety and depression scale (HADS). *Kathmandu Univ Med J (KUMJ)* 2015; **13**: 115–24
6. Sharma S, Thibault P, Abbott JH, Jensen MP. Clinimetric properties of the Nepali version of the pain catastrophizing scale in individuals with chronic pain. *J Pain Res* 2018; **11**: 265–76
7. Subedi A, Pokharel K, Sah BP, Chaudhary P. Association of preoperative pain catastrophizing with postoperative pain after lower limb trauma surgery. *J Psychosom Res* 2021; **149**: 110575
8. Park G, Kim CW, Park SB, Kim MJ, Jang SH. Reliability and usefulness of the pressure pain threshold measurement in patients with myofascial pain. *Ann Rehabil Med* 2011; **35**: 412–7
9. Myhre M, Romundstad L, Stubhaug A. Pregabalin reduces opioid consumption and hyperalgesia but not pain intensity after laparoscopic donor nephrectomy. *Acta Anaesthesiol Scand* 2017; **61**: 1314–24
10. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract Res Clin Anaesthesiol* 2007; **21**: 65–83
11. Bhusal BR, Bhandari N, Chapagai M, Gavidia T. Validating the Edinburgh postnatal depression scale as a screening tool for postpartum depression in Kathmandu, Nepal. *Int J Ment Health Syst* 2016; **10**: 71
12. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015; **156**: 1003–7
13. Jin J, Min S, Peng L, Du X, Zhang D, Ren L. No differences in the prevalence and intensity of chronic postsurgical pain between laparoscopic hysterectomy and abdominal hysterectomy: a prospective study. *J Pain Res* 2020; **13**: 1–9
14. Love RR, Ferdousy T, Paudel BD, et al. Symptom levels in care-seeking Bangladeshi and Nepalese adults with advanced cancer. *J Glob Oncol* 2016; **3**: 257–60
15. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; **393**: 1537–46
16. Goodchild CS, Nadeson R, Cohen E. Supraspinal and spinal cord opioid receptors are responsible for anti-nociception following intrathecal morphine injections. *Eur J Anaesthesiol* 2004; **21**: 179–85
17. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. *Br J Anaesth* 2013; **111**: 711–20
18. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; **152**: S2–15
19. McQuay HJ, Sullivan AF, Smallman K, Dickenson AH. Intrathecal opioids, potency and lipophilicity. *Pain* 1989; **36**: 111–5
20. Kerchner GA, Zhuo M. Presynaptic suppression of dorsal horn inhibitory transmission by mu-opioid receptors. *J Neurophysiol* 2002; **88**: 520–2
21. Dougherty PM, Staats PS. Intrathecal drug therapy for chronic pain: from basic science to clinical practice. *Anesthesiology* 1999; **91**: 1891–918
22. Nagasaka H, Awad H, Yaksh TL. Peripheral and spinal actions of opioids in the blockade of the autonomic response evoked by compression of the inflamed knee joint. *Anesthesiology* 1996; **85**: 808–16
23. Yamamoto T, Yaksh TL. Comparison of the anti-nociceptive effects of pre- and posttreatment with intrathecal morphine and MK801, an NMDA antagonist, on the formalin test in the rat. *Anesthesiology* 1992; **77**: 757–63
24. Yamamoto T, Nozaki-Taguchi N. Clonidine, but not morphine, delays the development of thermal hyperesthesia induced by sciatic nerve constriction injury in the rat. *Anesthesiology* 1996; **85**: 835–45
25. Nichols ML, Lopez Y, Ossipov MH, Bian D, Porreca F. Enhancement of the antiallodynic and antinociceptive efficacy of spinal morphine by antisera to dynorphin A (1-13) or MK-801 in a nerve-ligation model of peripheral neuropathy. *Pain* 1997; **69**: 317–22
26. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. *Anesthesiology* 2018; **129**: 590–607
27. De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. *Anesth Analg* 2005; **101**: 566–72
28. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* 2005; **103**: 813–20
29. Capdevila X, Moulard S, Plasse C, et al. Effectiveness of epidural analgesia, continuous surgical site analgesia, and patient-controlled analgesic morphine for postoperative pain management and hyperalgesia, rehabilitation, and health-related quality of life after open nephrectomy: a prospective, randomized, controlled study. *Anesth Analg* 2017; **124**: 336–45
30. Brennan TJ, Umali EF, Zahn PK. Comparison of pre- versus post-incision administration of intrathecal bupivacaine and intrathecal morphine in a rat model of postoperative pain. *Anesthesiology* 1997; **87**: 1517–28
31. Zahn PK, Gysbers D, Brennan TJ. Effect of systemic and intrathecal morphine in a rat model of postoperative pain. *Anesthesiology* 1997; **86**: 1066–77
32. Warncke T, Stubhaug A, Jørum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1997; **72**: 99–106
33. Warncke T, Stubhaug A, Jørum E. Preinjury treatment with morphine or ketamine inhibits the development of experimentally induced secondary hyperalgesia in man. *Pain* 2000; **86**: 293–303
34. Koppert W, Likar R, Geisslinger G, Zeck S, Schmelz M, Sittl R. Peripheral antihyperalgesic effect of morphine to heat, but not mechanical, stimulation in healthy volunteers after ultraviolet-B irradiation. *Anesth Analg* 1999; **88**: 117–22
35. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006; **104**: 570–87

36. Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? *Br J Anaesth* 1997; **78**: 311–3
37. Salengros JC, Huybrechts I, Ducart A, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J Cardiothorac Vasc Anesth* 2010; **24**: 608–16
38. Foadi N, Karst M, Frese-Gaul A, Rahe-Meyer N, Krömer S, Weilbach C. The improved quality of postoperative analgesia after intrathecal morphine does not result in improved recovery and quality of life in the first 6 months after orthopedic surgery: a randomized controlled pilot study. *J Pain Res* 2017; **10**: 1059–69
39. Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) – a systematic review. *Eur J Pain* 2009; **13**: 719–30

Handling editor: Nadine Attal