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Clinical effectiveness of transversus abdominis plane (TAP) bocks for pain relief after caesarean section: a meta-analysis

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Short title: TAP blocks for caesarean section

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ABSTRACT

Background: The effectiveness of transversus abdominis plane (TAP) blocks for acute pain relief after caesarean section, in comparison to normal practice, remains uncertain.

Methods: Electronic literature databases were searched from inception to May 2016 for randomised controlled trials that assessed the effectiveness of TAP blocks following caesarean section. Trials were eligible if comparisons were made against no block or placebo, and/or intrathecal morphine. Risk of bias was assessed using the Cochrane tool. Data for consistent outcomes were subject, where possible, to meta-analysis and presented as either mean differences with 95% confidence intervals or incidence of a particular event.

Results: Twenty published studies fulfilled our inclusion criteria. TAP blocks significantly reduced pain at rest both when compared with placebo or no TAP blocks (-0.96, 95% CI -1.67 to -0.25, P=0.008) and intrathecal morphine (1.10, 95% CI 0.59 to 1.60, P<0.0001). Both these comparisons showed the greatest improvement with pain on movement, (-1.58, 95% CI -2.69 to -0.47, P=0.005 and 1.35, 95% CI 0.76 to 1.94, respectively, P<0.00001). Morphine consumption was significantly reduced with TAP blocks when compared to placebo or no TAP blocks (-15.88, 95% CI -22.02 to -9.73, P<0.00001). This significance was lost when TAP blocks were both compared to intrathecal morphine (0.89, 95% CI -0.64 to 2.43, P=0.25) and given in co-administration (0.00, 95% CI -0.10 to 0.10, P=1.00).

Conclusion: TAP blocks provide effective analgesia after caesarean section; however, additional benefits are more difficult to demonstrate when long-acting intrathecal opioids are administered.

Keywords: Transversus abdominis plane block; TAP block; Caesarean section

Introduction

Acute pain from an abdominal incision can complicate birth by caesarean section (CS). Failure to achieve adequate pain control is one of the most common reasons for poor satisfaction among women who give birth by CS.[1] Caesarean section is a common surgical procedure, with an increasing prevalence. Approximately 166 000 CS are performed annually in England alone (data for 2014/2015).[2] Adequate postoperative analgesia hastens postoperative mobilisation, decreases maternal morbidity and facilitates bonding with the newborn.[3] Neuraxial opioids can provide effective pain relief for many hours after surgery, although their administration has a well-defined risk of side effects including nausea, pruritus, urinary retention and potential for delayed respiratory depression.[4] Alternative modalities of

pain relief offer the prospect of a beneficial reduction in the side effect profile with no loss in analgesic efficacy.[1]

The last two decades have seen peripheral nerve blockade gain prominence in the prevention and treatment of acute postoperative pain. The success of ultrasound-guided peripheral nerve localisation with nerve stimulation has fuelled new innovation in block technique and indication. These novel blocks can be performed with minimal risk of complications.[5, 6] Tranversus abdominis plane (TAP) block's mechanism of action requires anaesthesia to the sensory nerve supply of the anterior abdominal wall.[6-8] Blockade of sensory nerves is achieved in the neurofascial plane between the internal oblique and transversus abdominis muscles through a well-defined entrance at the triangle of Petit.[7, 8] The use of TAP blocks to alleviate pain after non-obstetric abdominal surgery has become established.[9] However, evidence from recently published clinical trials has shown encouraging results that suggest that TAP blocks are effective for treating postoperative pain following CS. This systematic review and meta-analysis collated data from all published randomised controlled trials of TAP blocks to assess its effectiveness in reducing patient-reported postoperative pain scores and reducing opioid use following CS.

Methods

The systematic review was based on a prospective protocol designed using widely recommended methods and reported to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[10-12] No institutional review board approval was needed for this review.

A comprehensive literature search strategy was used to search the following bibliographic databases, Embase, Medline and the Cochrane Library (CENTRAL), from database inception to May 2016. We adapted the search strategy used in a previous Cochrane review,[9] by replacing search terms pertaining to abdominal surgery with variations for CS as MeSH terms or text. The Clinical Trials registers found at www.clinicaltrials.gov, www.isrctn.com and the World Health Organisation (WHO) International Clinical Trials Research Platform (ICTRP) were searched to identify ongoing trials. The authors of these trials were contacted via email to ask if they would be willing to contribute unpublished data. Bibliographies of all relevant primary articles and reviews were hand searched to identify articles missed by the electronic searches. A comprehensive database was constructed using Reference Manager 12.0 (Thomson Reuters) to store all identified references. No language restrictions were applied.

Studies eligible for inclusion were selected in a two-step process. First, citations identified by the electronic database searches were screened. Full manuscripts were obtained for those citations that met, or potentially met, predetermined inclusion criteria. Two reviewers then independently inspected the manuscripts to confirm that they fulfilled the following criteria:

1. Population: Women undergoing elective caesarean section
2. Interventions: TAP blocks using any local anaesthetic agent, alone or in addition to intrathecal morphine (ITM).
3. Comparator: No or placebo TAP blocks, alone or in addition to ITM. Studies comparing different doses of local anaesthetic in TAP blocks were excluded unless there was a control group.
4. Outcomes: Pain scores (at rest and movement), opioid consumption, complications (nausea, vomiting, pruritus) and maternal satisfaction.
5. Study design: Randomized controlled trial (RCT) where the action of TAP block could be assessed independently of any ITM administered.

We extracted data on study characteristics, methods and results on to a pre-designed pro-forma in duplicate.

All manuscripts selected for inclusion were assessed using the risk of bias tool developed by the Cochrane Collaboration.[9] A study was considered to be of high quality if it provided evidence of adequate randomisation sequence generation and allocation concealment, if blinding was used, if there were minimal missing outcome data or it was adequately addressed, and if the published paper was free of selective reporting and free of other biases.

If a trial comparing various doses of TAP blocks was amongst those trials thought to be eligible for inclusion, every attempt was made to include these data. However, in these circumstances, a form of data manipulation was necessary before the data were used. A validated and recognized formula used by the Cochrane Collaboration enabled us to combine data from the various dosage arms and compare these against the placebo/control arm.

Trials were grouped according to the question they addressed: a) the effectiveness of TAP blocks in the absence of ITM; b) comparison of ITM against TAP blocks; and c) the addition of TAP blocks to ITM. Where trials addressed more than two questions, the appropriate groups' data were included in each comparison. No further subdivision of questions by technique, local anaesthetic used or dose was undertaken.

Statistical analysis

Outcome data were extracted from all included studies, as number of women, means and standard deviations for continuous variables and as proportions for dichotomous outcomes. If data were provided in another format, the author of the trial was contacted to ask if they could provide raw data. Failing this, every attempt was made to convert these values to allow the greatest amount of data to be combined. Outcome data were used to generate forest plots. Pain scores presented as a visual analogue scale (VAS) score were standardized to a 0–10 point continuous scale. Where a VAS score was presented as median and interquartile range (IQR) and the group size was >20, these were assumed to follow a normal distribution, with the median assumed to be the mean and standard deviation=IQR/1.35. Data transformed in this way were added to meta-analyses in a secondary sensitivity analyses. Cumulative opioid consumption was considered, with opioid drugs other than morphine converted to morphine equivalent doses, using a published equivalence formula.[13] Incidence of postoperative nausea and vomiting (PONV) was variously reported as one entity, or as separate conditions. In the latter case, we used nausea data to avoid double counting. Pruritus was also measured in a variety of ways. Where possible, data were collapsed into a dichotomous measure of present or absent. All statistical analyses were performed in Review Manager 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2011). Heterogeneity was described by the I^2 statistic and where significant, a random effects model was used to produce the summary estimate.

Results

A total of 187 citations were identified through the electronic literature database searches. Of these, 146 were excluded after screening of titles and abstracts. A further 21 citations were discarded upon closer inspection, being either duplicate publications, not using a study design of interest (letters, reviews etc.), or not using a relevant intervention. The remaining 20 articles were included in the systematic review (Fig. 1).[14-33] Three abstracts were included in the systematic review,[19,31,32] and we obtained unpublished data from one author.[32] A search of the Clinical Trials register identified six relevant ongoing trials. However, none of these trials were at a suitable stage to contribute unpublished data.

Table 1 provides a summary of the characteristics of the included published trials in addition to a breakdown of the quality criteria per trial. A table describing the ongoing studies is presented in Appendix A. Eleven trials evaluated the efficacy of TAP blocks versus placebo TAP blocks [14-17, 19-22, 30, 31,33] and three against no TAP blocks (only standard care),[18, 23, 29] all

of these in the absence of ITM. Kagwa et al. randomised patients to TAP blocks or 'sham' TAP blocks. Sham blocks involved pressing a transducer with a needleless syringe over each flank. We consider this to be equivalent to 'No TAP blocks'.[31] Three trials directly compared ITM with TAP blocks by employing ITM plus placebo TAP blocks in one group and intrathecal placebo and TAP blocks in the other,[22, 24, 25] and five trials evaluated the addition of TAP blocks to ITM via the use of a placebo TAP injection.[22, 26-28, 32] The trial by McMorrow et al. undertook all three comparisons. The trial by Puddy et al. reported comparisons with intrathecal diamorphine and was excluded from the meta-analysis since the analgesic profile of intrathecal diamorphine is substantially different to ITM, particularly in duration of action and side effects. These trials were retained in the systematic review. Sixteen of the 20 trials involved women undergoing an elective CS,[17-29, 31, 32,33] with the remainder not specifying the nature of the CS. Trials involving emergency CS only were excluded since these women may have laboured before CS, and would be more likely to have had the CS performed under epidural anaesthesia and may have a substantially different postoperative pain experience. There was an intention to perform bilateral TAP block in all trials, although this was not explicitly stated by Kagwa et al.[31] An ultrasound-guided technique was used in 15 studies.[14-17, 21, 23-28, 30-33] and four trials used the anatomical landmark technique [18, 20, 22, 29] whilst in the final study, the approach was unclear.[19]

Bupivacaine was the local anaesthetic of choice in eight trials [14, 16, 18, 22, 24, 32, 29, 31] whilst nine trials used ropivacaine; [15, 20, 21, 25-28, 30,33] three others used levobupivacaine.[17, 19, 23] Eighteen trials performed CS under spinal (or combined spinal-epidural) anaesthesia, [14-17, 19-22, 24-32,33] while general anaesthesia was used in two trials.[18, 23]

A varied mix of supplementary postoperative analgesia regimens was used. Pain scores were reported in all included trials; however, it was not possible to use data from every trial due to inconsistencies in the way data were presented or pain symptoms described. Where the primary outcome was explicitly stated, the most frequently employed was morphine consumption (or equivalent), being specified by nine trials.[14, 15, 17, 20, 23, 25, 29, 30, 33] Other commonly measured outcomes included, pain scores at rest, [18, 31] pain on movement, [22, 26-28, 31] wound hyperalgesia [16] and time to first analgesic request.[24, 32] McKeen et al. chose to have four primary outcomes, pain at rest, pain on movement, quality of recovery and cumulative opioid consumption.[21] The abstract by Hoydonckx et al did not provide details of the primary outcome.[19]

A detailed breakdown of the quality of the trials is given in Table 1. The majority provided adequate information to assess quality criteria. Two studies were only available in

abstract format and attempts to contact the corresponding authors for further information were unsuccessful.[19,31] Strict, random group allocation concealment was a feature of 13 studies, whilst 19 were blinded. Only 10 trials provided a satisfactory level of detail to show that their trial was free of attrition and other biases. We would have expected all women to have been followed up for the primary outcome, irrespective of protocol compliance, but whether this was done was unclear in seven studies. There were inherent blinding complications in the four trials that compared TAP blocks to no TAP blocks, but these trials have indicated that investigators and patients were blinded to treatment allocation.[18, 23, 29, 31] Patients in the no treatment groups in the Eslamian et al.[18] Kagwa et al.[31] and Tan et al.[23] trials received no injections; therefore the skin was not punctured. Tan was able to blind patients by placing a pressure dressing over the site where the TAP block would have been injected.[23] This is similar to treatment of patients in the control arm of the Srivastava et al trial,[29] who did not receive a block, but they still had their skin punctured on both sides by palpating the triangle of Petit. Patients in this trial, had pressure dressings applied to their abdominal wounds that covered the skin puncture sites.[29]

While pain at rest, pain on movement and morphine consumption remain our three main outcomes, data on other outcomes, including PONV and pruritus have been tabulated in Table 2. There were statistically significant reductions in the incidence of PONV at 24 h amongst both the TAP blocks versus control (OR 0.53, 95% CI 0.29 to 0.97, *P*=0.04), and the TAP blocks versus ITM comparisons (OR 0.24, 95% CI 0.09 to 0.64, *P*=0.004). Both these findings in favour of the TAP blocks arm, were based on data from seven trials (n=354) and two trials (n=106), respectively. Occurrence and severity of pruritus were significantly increased in those receiving ITM with TAP blocks (OR 2.63, 95% CI 1.16 to 5.95, *P*=0.02).[22, 26, 27] Forest plots have been generated for these outcomes but are displayed in Appendix B.

1. Pain at rest

TAP blocks versus control (or no treatment)

Nine out of the 14 trials that compared TAP blocks with a control provided disaggregated data on pain at rest.[14, 16-18, 20-23, 29] whereas pain scores could not be disaggregated in one trial,[15] and the abstracts by Hoydonckx et al.[19] and Kagwa et al.[31] did not provide useable data. Sriramka et al. reported overall VAS scores rather than pain scores specific to pain at rest and/or movement.[30] They reported that patients randomised to TAP blocks had lower pain scores on a VAS (median 26 vs. 47mm, *P*=0.008). Attempts to contact the author for unpublished data were unsuccessful. Mankikar et al. also reported overall pain scores, in the

form of a figure. We were unable to accurately measure individual scores. Attempts to contact the author for numerical data were unsuccessful.[33] Pooled results for pain at rest 6 h postoperatively favoured TAP blocks (mean difference -1.43, 95% CI -2.82 to -0.04, *P*=0.04). However, this significance disappeared by 24 h (mean difference -0.63, 95% CI -1.38 to 0.11, *P*=0.10) (Fig. 2). Overall results, combining both time points indicate that TAP blocks, when compared to control, are effective for pain at rest (mean difference -0.96, 95% CI -1.67 to -0.25, *P*=0.008).

ITM versus TAP blocks

Results from the two trials with clearly reported data[22, 25] showed significant effect in favour of ITM when TAP blocks and ITM were measured at 6 h (mean difference 1.17, 95% CI 0.46 to 1.87, *P*=0.001) this significance continued at 24 h postoperatively (mean difference 1.03, 95% CI 0.31 to 1.74, *P*=0.005) (Fig. 3). Overall results support these findings (mean difference 1.10, 95% CI 0.59 to 1.60, *P*<0.0001). Data from the trial by Kanazi et al. could not be included in the forest plot as it was non-normally distributed and it considered both somatic and visceral pain at 2 and 4 h postoperatively.[24] Pain scores at rest were not significantly different at 6 and 24 h.

ITM with or without TAP blocks

Five trials provided data which were used to produce the forest plot in Fig. 4.[22, 26-28, 32] Although Puddy et al. provided data, this was not included in the meta-analysis as their comparison involved diamorphine. Therefore, based on data from the remaining four trials, short-term results suggest that a combination of ITM and TAP blocks are more effective than ITM alone in the 6h after surgery (mean difference -0.50, 95% CI -0.92 to -0.08, *P*=0.02); however, this effect is not sustained at 24 h (mean difference 0.12, 95% CI -0.33 to 0.58, *P*=0.60). Combining data over both time points suggest no effect (mean difference -0.21, 95% CI -0.52 to 0.10, *P*=0.18).

2. Pain on movement

TAP blocks versus control (or no treatment)

Nine trials provided data for these meta-analyses.[14, 16-18, 20-23, 29] TAP blocks were no more effective than control for treating pain on movement 6 h postoperatively (mean difference -1.65, 95% CI -3.52 to 0.22, *P*=0.08) (Fig. 5). At 24 h, a statistically significant effect was seen in favour of TAP blocks (mean difference -1.54, 95% CI -3.02 to -0.05, *P*=0.04). Combining

data from both time points for an overall effect followed this significant trend (mean difference -1.58, 95% CI -2.69 to -0.47, *P*=0.005). Abstracts by Hoydonckx et al.[19] and Kagwa et al.[31] did not contain useable data. Other trials unable to contribute data were Belavy et al.,[15] Sriramka et al.[30] and Mankikar et al.[33] who reported overall pain scores, rather than differentiating between pain at rest and on movement.

ITM versus TAP blocks

As with pain at rest, data for this outcome were only available in a usable form in two trials.[22, 25] Pooled results from these trials found a statistically significant effect in favour of ITM for alleviating pain on movement at both 6 h (mean difference 1.36, 95% CI 0.51 to 2.21, *P*=0.002), and 24 h (mean difference 1.34, 95% CI 0.51 to 2.17, *P*=0.002) (Fig. 6). Overall pooled results using both time points, corroborate this finding (mean difference 1.35, 95% CI 0.76 to 1.94, *P*=0.00001).

ITM with or without TAP blocks

All five trials included in this comparison provided data for this outcome. However, it was only possible to use data from four trials, after the exclusion of data from Puddy et al.[22, 26-28] A statistically significant effect was seen at 6 h, which showed that a combination of both ITM and TAP blocks were more effective than ITM alone (mean difference -0.89, 95% CI -1.47 to -0.31, *P*=0.002) (Fig. 7). This effect, however, could not be detected at 24 h (mean difference 0.28, 95% CI -0.27 to 0.82, *P*=0.32). The overall pooled effect was not statistically significant (mean difference -0.27, 95% CI -0.67 to 0.12, *P*=0.18).

3. Morphine consumption

TAP blocks versus control (or no treatment)

Three trials each provided morphine consumption data at 2, 6 and 12 h postoperatively and seven at 24 h.[14, 15, 17, 20, 21, 23, 33] Pooled data at all four time points found a statistically significant lower morphine consumption in the TAP blocks group (Fig. 8): 2 h (mean difference 3.23mg, 95% CI -5.37 to -1.09, *P*=0.003); 6 h (mean difference 12.27mg, 95% CI -13.76 to -10.77, *P*<0.00001); 12 h (mean difference 19.86mg, 95% CI -27.33 to -12.39, *P*<0.00001); and 24 h (mean difference 21.27mg, 95% CI -32.18 to -10.36, *P*=0.0001). Overall pooled results across all time points, follow a similar trend (mean difference 15.88mg, 95% CI -22.02 to -9.73, *P*<0.00001). Seven trials were unable to contribute data. Bollag et al.,[16] McMorrow et al.,[22] Sriramka et al.[30] and Srivastava et al.[29] presented the time points as

ranges rather than at single time-points. Therefore, we were unable to combine this with the cumulative data. Eslamian et al. provided data in a format that did not allow for merging with other data.[18] The abstracts by Hoydonckx et al and Kagwa et al did not provide data.[19 31]

ITM versus TAP blocks

Of the three trials reporting morphine or morphine equivalent dosage, only data from Loane et al.[25] were useable, therefore a forest plot is not provided. They reported no difference in morphine consumption between the groups at 0–2 h (mean difference 0.70 mg, 95% CI -1.59 to 0.20, *P*=0.13), 2–6 h (mean difference 0.62 mg, 95% CI -0.87 to 2.11, *P*=0.42) and 6–10 h (mean difference 0.85 mg, 95% CI -0.33 to 2.03, *P*=0.16).[25] However, this difference became statistically significant between 10–24 h, with lower use in the ITM group, (mean difference 4.80 mg, 95% CI 1.76 to 7.84, *P*=0.002). Both McMorrow et al.[22] and Kanazai et al.[24] noted a statistically significant difference in morphine or equivalent opioid consumption between 6–12 h but at no other time points. These two trials provided cumulative data, so were not combined with data from Loane et al.[25]

ITM with or without TAP blocks

A forest plot was unsuitable for this comparison and outcome as only Costello et al provided data.[26] They showed that morphine consumption remained unaffected at both 24 h (mean difference 0.00mg, 95% CI -0.30 to 0.30, *P*=1.00) and 48 h (mean difference 0.00mg, 95% CI -0.10 to 0.10, *P*=1.00).[26] McMorrow et al.[22] did not observe a difference in morphine consumption at any time point, reporting a median consumption of 5 mg and 6 mg in the ITM and TAP blocks, and ITM and placebo TAP blocks, respectively, at 24 h. Data from Lee et al.[27] and Singh et al.[28] were not in a compatible format and therefore were not included. Data provided by Puddy et al again could not contribute to the meta-analysis.[32]

4. Maternal Satisfaction

Due to variation in how satisfaction with analgesia was captured and reported, no meta-analyses were attempted and results are explained narratively.

TAP block versus control (or no treatment)

Satisfaction was measured in a variety of ways but was higher for TAP blocks than controls in 6 RCTs,[14, 15, 22, 23, 17, 29] although only statistically significant in four studies,[14, 15, 23, 29] whilst

there was less satisfaction within TAP blocks in one study.[21] The remaining seven studies either did not measure or report satisfaction with analgesia.

ITM versus TAP blocks

Kanazi et al.[24] presented satisfaction data on a three-point scale: highly satisfied, satisfied and dissatisfied. In the ITM and placebo TAP blocks group 26 of 28 women were either satisfied or highly satisfied, compared to 22 of 29 women in the intrathecal placebo and TAP blocks group. McMorrow et al.[22] reported a non-significantly higher median satisfaction score in the ITM and placebo TAP blocks group at all time points. Satisfaction was not measured by Loane et al.[25]

ITM with or without TAP block

Plotting of data from two trials found no overall statistically significant difference between the two groups.[26, 28] Like other comparisons, there was no statistically significant difference between groups in the McMorrow et al trial.[22] Lee et al[27] reported more patients were satisfied with TAP blocks given in conjunction with ITM rather than placebo TAP blocks and ITM. However, these values were not statistically significant at 24 and 48 h. Puddy et al did not report satisfaction as an outcome.[32]

Discussion

The evidence generated by this meta-analysis demonstrates that TAP blocks are an effective intervention in providing acute pain relief after CS. Whilst they may not confer much additional analgesia when intrathecal opioids are used; they are at least as effective. Our findings support the premise that TAP blocks could offer particular advantages in the context of general anaesthesia for CS when the only alternative is systemic opioid analgesia.

The greatest analgesic effect was seen in women given TAP blocks in the absence of ITM. Pooled results found that TAP blocks were more effective than control at alleviating pain at rest, which was reduced by a clinically meaningful 3.5 points out of 10, [34]although this effect was diminished by 24 h. Intrathecal morphine was no more beneficial than TAP blocks for pain at rest. When TAP blocks and ITM were combined, the effect was superior in the short term to ITM alone, but again this effect was not sustained at 24 h. TAP blocks were more effective in alleviating pain on movement compared to control. However, when TAP blocks were compared to ITM, this effect was lost. This was also the case when TAP blocks and ITM were compared to ITM alone.

TAP blocks alone, when compared to control, were again the most effective modality, in reducing postoperative opioid consumption, in this case reducing consumption by more than half. However, when compared to ITM, this short-term benefit was lost. There was no difference between TAP blocks and ITM at 2, 6 and 10 h postoperatively. However, ITM was superior to TAP blocks at 24 h. When the two were combined, and compared against ITM, no difference was found. These findings support the premise that TAP blocks offer particular advantages when spinal opioids are not administered.

TAP blocks were superior in reducing the incidence of PONV when compared to ITM but not when compared to control. This effect must be taken in the context of any differences in opioid consumption. A combination of TAP blocks and ITM, was no more effective than ITM alone, suggesting that the administration of neuraxial morphine is the most potent arbiter of the prevalence of PONV after CS.

No evidence of differential rates of pruritus were observed between women receiving TAP blocks, ITM or control, whilst the addition of TAP blocks to ITM increased the rate of pruritus. There was considerable variation in the pooled rates of pruritus in the TAP blocks group from 30-62%, and those only receiving ITM, in the three comparisons, making it imprudent to rank the groups for this adverse event.

More women were satisfied with TAP blocks than control. However, when TAP blocks were compared with ITM, a greater number of women preferred ITM. When these two treatment options were combined, no difference in satisfaction was found. Whilst maternal satisfaction with childbirth is increasingly recognised as a vital aspect of care, maternal satisfaction with planned CS is very high and any effect of the addition of TAP blocks may be difficult to detect.

The strength of our review lies in the systematic methodology with which trials were identified and their quality appraised. Risk of bias was assessed using widely accepted Cochrane collaboration tools. The quality of included trials in general was good. The inclusion of three trials only available as abstracts [19, 31, 32] almost certainly contributed to worsening the overall impression of quality of the included trials.

A further strength is that we have tried to reflect clinical practice as much as possible. Although intrathecal diamorphine is widely used in UK practice, the single trial using diamorphine in their intervention arm was excluded from analysis. This was justifiable since ITM and diamorphine are quite distinct in their pharmacology, effectiveness and duration of action. The side effect profiles of the two agents also differ substantially. Diamorphine is not clinically available in USA or mainland Europe. In this sense, UK practice is unusual. It is

hoped that by retaining this study in the systematic review, our findings are relevant to as wide an audience as possible.

Several sources of heterogeneity were identified. Despite a certain degree of standardisation amongst the population (most patients were undergoing an elective CS), the intervention was a source of heterogeneity. All trials fell into two broad groups, those that used ultrasound-guided techniques and those that used anatomical landmark techniques. Further sources of heterogeneity were the postoperative analgesia regimens, which varied considerably. The local anaesthetic agent used to perform TAP blocks was not standard amongst the trials. The choice and dose of the local anaesthetic was much more varied. Once trials had been separated into their comparisons, further separation according to type of local anaesthetic agent used would not have been possible with the limited number of trials available. Further heterogeneity was mitigated, by keeping methods of data synthesis consistent; for example conversion of tramadol consumption data to morphine consumption. We tried to incorporate heterogeneity by using a random effects model where appropriate, rather than stepwise exclusion of outliers, again due to the small number of studies.

Due to variations in how PONV outcomes were measured, we made the following assumption, in order to be able to combine as much data as possible. Some trials provided PONV data, which was a combined score of nausea and vomiting, others described separate scores. For these trials, we used nausea data alone, since using data for both nausea and vomiting would risk some patients being double-counted.

As our review and others have highlighted, TAP blocks are an effective analgesic intervention for acute pain following CS. Our meta-analysis also generates further compelling evidence for the effectiveness of intrathecal opioids in providing pain relief after CS. Our analysis does not support the assertion that TAP blocks replace the need for intrathecal opioid analgesia, thereby reducing the incidence of spinal-opioid-related side effects, nor favour a widespread change in practice. Nonetheless, TAP blocks offer particular advantages in the context of CS where neuraxial opioids are not utilised.

The results of our review are supported by those found by other systematic reviews.[35,36] Abdallah et al found that TAP blocks were more effective than placebo for providing analgesia.[35] They were also superior at reducing the need for morphine in the first 24 h after surgery, based on an analgesic regimen that excluded ITM. Mishriky et al. corroborated these findings.[36] This review included a third comparator, ITM and reported that postoperative analgesia was significantly improved by TAP blocks in women who had not received ITM. However, this benefit was lost in women who had received ITM. Improved

analgesia was seen with ITM, compared to TAP blocks alone. A further narrative review, by Sharkey et al.[37] reinforced this sentiment which was convergent in opinion with the Mishriky review.[36] Our results are broadly convergent with the other evidence synthesis in the field. Fusco et al. found that TAP blocks reduced both opioid consumption and opioid related side effects. There were also improvements in postoperative pain and patient satisfaction with TAP blocks.[38] Reviews by Ripolles et al.[39] and Baeriswyl et al.[40] are broader systematic reviews, focussing on all types of abdominal surgery, including CS. These reviews confirmed the analgesic efficacy provided by TAP blocks.

While certain parallels can be drawn between our review and those by Abdallah and Mishriky, our review provides a more comprehensive and accurate picture of the current evidence by encompassing all relevant trials up to the present day. This includes those found by Abdallah and Mishriky but also identifying trials published after their search date. Our review acts as a summation of other relevant reviews. While the reviews by Abdallah and Mishriky consisted of sample sizes of 312 and 524, respectively, the current review involves data from 1293 women.

This review has highlighted gaps in the evidence, which could be subjected to future study. Caesarean section is a common intervention, which is becoming more prevalent. Therefore, research in this area is pertinent to a large population. The potential benefit of TAP blocks over a control for post-CS analgesia, in the absence of ITM, is supported by several trials. Future research should focus on assessing the effectiveness of ITM compared to and in addition to TAP blocks. Larger, well designed, adequately powered trials are needed to achieve this. Three local anaesthetic agents were used in the trials included in this review, with bupivacaine being the most common. As our results have shown, combining TAP blocks and ITM has beneficial outcomes particularly for pain at rest. Assessing whether lower doses of this treatment option has implications for improved analgesia and reduction of opioid-induced side effects is also another area worth pursuing.

The findings of our review have shown that TAP blocks are most effective in relieving postoperative pain following a CS delivery, in patients who have not received ITM. There is much more uncertainty surrounding the use of TAP blocks instead of ITM or in addition to it. Future trials should consider this an area for exploration.

Disclosure

MJW is a member of the Editorial Advisory Board of the International Journal of Obstetric Anaesthesia. No other disclosure of interests is declared. No funding was sought to undertake this review

Contribution to authorship

JPD conceived the idea for the review. RC performed literature searches for published evidence, while LS searched for ongoing trials. RC and LS screened results of their respective searches. JPD screened citations thought to be eligible for inclusion. RC and JPD undertook double data extraction. Statistical analysis of the results was performed by RC. Initial and all subsequent drafts of the manuscript were prepared by RC. LS produced tables for inclusion in the manuscript. MJW provided clinical guidance when needed and assisted in writing the manuscript. All authors read the final manuscript and provided comments and feedback.

1. *The references are not correct. Please check Daniels et al (ref 33). Should this be Mankikar (currently ref 40)? Please check and renumber references in both text and reference list.*
   25/7/2016 – Manikakar is now ref 33, and Daniels is 40. This should be reflected throughout
2. ***19/07/2016 - You are correct. Mankikar should be ref 40, and Daniels should be 33. These changes have been made throughout. So references for Mankikar (40) and Daniels (33), should now all match.***
3. *Also the references are not presented in the style requested in the journal's Guide for Authors and several are incomplete. Please check and correct where necessary.*
   References have been amended using the Guide for Authors. For example, issue numbers for journal articles have been removed as has writing the journal name in italics. All incomplete references have also been corrected
4. *Please include a website address after references not in scientific journals.*
   This has also been corrected following Guidance for Authors

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Supplementary material

Supplementary data associated with this article can be found in the online version at doi 10.1016/j.ijoa20xx.xx.xxx

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