Introduction

Optimizing perioperative analgesia is imperative to a smooth recovery following major abdominal surgery (1). Multiple guidelines, including enhanced recovery after surgery (ERAS) recommendations, encourage multimodal analgesia and avoidance of opioids (2). However, postoperative pain management can be challenging and as such opioids are frequently needed (3-5). Opioid medications come with a range of adverse effects, and resultantly the choice of opioid to administer should be made responsibly.

A recent meta-analysis has found buprenorphine to...
be an effective analgesic for managing acute pain (6). Being a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist, it is largely accepted that buprenorphine has favorable adverse effect profile relative to morphine (7,8). Furthermore, buprenorphine has the significant benefit of a low, if not absent, risk of abuse and is employed to treat opiate addiction (9,10). Buprenorphine can be administered via multiple means including the convenient sublingual route. It therefore presents the opportunity to avoid intravenous opiate analgesia in the nil-per-oral patient and possible facilitation of earlier cessation of patient-controlled opioid analgesia (PCA). The preclusion of the need for intravenous lines and PCA equipment may allow earlier mobilization and a reduced infection risk (11). Due to its high affinity for mu-opioid receptors, buprenorphine has a longer half-life than morphine and requires less frequent dosing (12-14).

Given the many potential advantages of buprenorphine, we sought to investigate its effectiveness in managing pain following abdominal surgery compared to morphine. We also examined buprenorphine’s opioid-related side effects relative to morphine. This was achieved by means of a systematic review and meta-analysis of randomized controlled trials.

Methods

Search strategy

Five databases (Cochrane trials registry, SCOPUS, Medline, CINAHL and Web of Science) were systematically searched from the inception of the databases until May 2019. This search was conducted by two independent reviewers (L White & A Hodge) searching the terms (I) “buprenorphine” AND “acute pain”; (II) “buprenorphine” AND “post-operative pain”; (III) “buprenorphine” AND “surgical pain”. A manual reference check and citation check of included papers was performed to identify any additional studies.

Study eligibility

For a study to be included, the authors were required to report on the use of buprenorphine versus morphine in the management of acute pain after “major abdominal surgery” in the inpatient hospital setting. Given the lack of consensus in the literature, we defined major abdominal surgery as surgery involving the abdominal cavity, abdominal wall or abdominal organs PLUS an expected duration greater than 60 minutes or involving large abdominal wall incisions for example a laparotomy.

Only randomized controlled trials (RCTs) were eligible for inclusion and there were no language criteria for exclusion. Two reviewers (L White & A Hodge) independently assessed each study for inclusion in this systematic review.

Morphine is a well-studied and understood opiate and was chosen as a “treatment-as-usual” control group. Studies investigating the use of buprenorphine for chronic pain or opioid addiction were excluded.

Data extraction

Two reviewers (LW and AH) independently extracted data from each article that met the inclusion criteria. The data extracted from each study included the study design, patient characteristics and clinical outcome results. The data collected by each reviewer was then compared for homogeneity.

Clinical outcome measures

Our a priori primary outcomes of interest were analgesic effect [as measured by visual analogue scale (VAS)] and rescue analgesia requirement. The secondary outcomes were incidence of respiratory depression, incidence of sedation, nausea, vomiting, dizziness and hypotension.

Level of evidence, risk of bias & outcome level of evidence ranking

Each article was evaluated using the Centre for Evidence Based Medicine (CEBM): Levels of Evidence Introduction Document (15). These studies were then assessed for risk of bias and methodological quality using the Cochrane Collaboration’s tool for assessing the risk of bias (16). The results from each study were then grouped by outcome. Where quantitative analysis was unfeasible, qualitative analysis was performed.

Statistical analyses

The combined data was analyzed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). Odds ratios (OR) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes using the
Mantel-Haenszel model with random effects. Weighted mean difference (WMD) with 95% CI was calculated for continuous outcomes. Heterogeneity was assessed using the $I^2$ statistic, with an $I^2 > 50\%$ indicating significant heterogeneity. P value of <0.05 provided evidence of significant OR and WMD. A P value of <0.10 was used to demonstrate heterogeneity of intervention effects. A sensitivity analysis was performed on each outcome by separating the adult and pediatric studies.

**Reporting**

This study was reported in line with PRISMA guidelines (17).

**Results**

**Literature search results**

The initial systematic literature search yielded 2,532 citations and a further 16 citations were identified through a manual citation and reference search of relevant articles (Figure 1). Following the removal of duplicates, animal studies and non-clinical studies, 361 citations remained. Of these, 348 abstracts were screened and 59 full texts were retrieved for review. Eleven articles met the inclusion criteria (Figure 1). These 11 studies included 764 patients (12-14,18-25). All studies investigated the management of post major abdominal surgery pain, comparing buprenorphine to morphine (Table 1). Five studies met the criteria for high quality RCTs, leaving six low quality RCTs (Figure 2).

**Primary outcomes**

Post-operative pain was measured using a variety of endpoints including various pain scores and drop-out rate as a consequence of pain. Pain scores from 1 to 6 hours were measured by six studies. The outcomes varied between these papers, with 3 demonstrating no difference and 3 showing lower pain scores with buprenorphine (12,13,20,22,24,25). A quantitative analysis was unable to be performed on these studies. Three studies investigated pain at 6 to 12 hours and revealed a significant improvement in analgesia with buprenorphine (VAS WMD =−0.75; 95% CI: −1.16 to −0.34; $I^2=49\%$; $P=0.0003$). Four studies assessed pain at 24 hours, at which time there was no difference in experienced pain (VAS WMD =−0.41; 95% CI: −1.04 to 0.22; $I^2=97\%$; $P=0.21$) (13,18,19,21). The same four studies showed no difference at 48 hours (VAS WMD =0.03; 95% CI: −0.84 to 0.90; $I^2=97\%$; $P=0.94$) (13,18,19,21).

Nine studies investigated the use of rescue analgesia (13,14,18,19,21-25). Five used incidence of rescue analgesia use and four used the cumulative totals of

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**Figure 1** Database and study selection flow chart.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients (buprenorphine/morphine) and types of surgeries included</th>
<th>Mean age (buprenorphine/morphine) (years)</th>
<th>Mean weight (buprenorphine/morphine) (kg unless stated otherwise)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley 1984 (12)</td>
<td>41/39 Cholecystectomy and abdominal hysterectomy</td>
<td>40.7±9.0/ 40.8±8.3</td>
<td>65.7±16.8/ 63.0±10.9</td>
<td>Intravenous buprenorphine 4–6 μ/kg versus intravenous morphine 0.15 mg/kg. Repeated dosing</td>
<td>Pain Nausea Respiratory depression Sedation Nausea Vomiting Dizziness</td>
</tr>
<tr>
<td>Cook et al. 1982 (13)</td>
<td>23/24 Types of abdominal surgery not specified</td>
<td>48±10/45±11</td>
<td>66±8/63±13</td>
<td>Intramuscular buprenorphine 0.3 or 0.45 mg or intramuscular morphine 10 or 15 mg. Repeated dosing</td>
<td>Pain Respiratory depression Hypotension</td>
</tr>
<tr>
<td>Cuschieri et al. 1984 (18)</td>
<td>39/41 Upper and lower abdominal incisions</td>
<td>58±14/52±15</td>
<td>63±13/63±10</td>
<td>Intramuscular morphine 10 mg or buprenorphine 0.3 mg intramuscular followed by sublingual buprenorphine 0.4 mg. Repeated dosing</td>
<td>Pain Respiratory depression Sedation Nausea Vomiting</td>
</tr>
<tr>
<td>Derbyshire et al. 1984 (19)</td>
<td>35/30 Cholecystectomy, hysterectomy, inguinal herniorrhaphy</td>
<td>48.8 (1.9 SEM)/ 47.7 (2.0 SEM)</td>
<td>69.9 (2.5 SEM)/ 64.9 (1.4 SEM)</td>
<td>Sublingual buprenorphine 400 pg or oral morphine sulphate 20 mg. Repeated dosing</td>
<td>Pain Respiratory depression Dizziness Nausea</td>
</tr>
<tr>
<td>Dobkin et al. 1977 (20)</td>
<td>39/40</td>
<td>0.2 mg =47/ 5 mg =44; 0.4 mg =45/ 10 mg =45</td>
<td>0.2 mg =70/ 5 mg =73; 0.4 mg =67/ 10 mg =72</td>
<td>Intramuscular buprenorphine 0.2 mg vs. intramuscular morphine 5 mg</td>
<td>Pain</td>
</tr>
<tr>
<td>Ellis et al. 1982 (21)</td>
<td>35/36 Cholecystectomy, hysterectomy, inguinal herniorrhaphy</td>
<td>Cholecystectomy 51.3±4.3/53.7±3.5; herniorrhaphy 51.7±2.7/54.7±2.5</td>
<td>Cholecystectomy 64.3±3.6/66.9±2.1; herniorrhaphy 72.0±2.1/75.5±2.3</td>
<td>Sublingual buprenorphine 0.4 mg vs. intramuscular morphine 10 mg IM. Repeat dosing</td>
<td>Pain Sedation</td>
</tr>
</tbody>
</table>
## Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients (buprenorphine/morphine) and types of surgeries included</th>
<th>Mean age (buprenorphine/morphine) (years)</th>
<th>Mean weight (buprenorphine/morphine) (kg unless stated otherwise)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaitini et al. 1996 (22)</td>
<td>26/26 Open prostatectomy</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Sublingual buprenorphine 0.4 vs. 1 mg morphine PCA. Repeat dosing</td>
<td>Pain, Hypotension</td>
</tr>
<tr>
<td>Green et al. 1985 (23)</td>
<td>26/30 Types of abdominal surgery not specified- upper and lower abdominal</td>
<td>38.4/41.4</td>
<td>62/64.8</td>
<td>4.5 μg/kg of buprenorphine or 0.15 mg/kg of morphine intramuscular. Repeat dosing</td>
<td>Hypotension, Rescue analgesia, Pain, Nausea, Vomiting, Sedation, Dizziness</td>
</tr>
<tr>
<td>Kay 1978 (24)</td>
<td>16/17 Types of abdominal surgery not specified</td>
<td>50.5±4.7/46.7±3.8</td>
<td>65.0±2.7/65.8±2.8</td>
<td>Buprenorphine 0.3 mg intravenous vs. 10 mg morphine intravenous. Single dose</td>
<td>Pain, Time to analgesia, Sedation, Nausea, Vomiting</td>
</tr>
<tr>
<td>Oifa et al. 2009 (25)</td>
<td>30/30 Gastrectomy, large bowel resection, partial pancreatectomy</td>
<td>61.6±10.2/63.1±15.2</td>
<td>73.3±18.2/69.8±12.5</td>
<td>Intravenous buprenorphine vs. morphine, PCA basal bolus dosing</td>
<td>Pain, Nausea, Rescue analgesia</td>
</tr>
<tr>
<td>Payne et al. 1987 (14)</td>
<td>30/30 Types of abdominal surgery not specified-laparotomy</td>
<td>&gt;18 years old</td>
<td>Not stated</td>
<td>Intramuscular 0.15 mg/kg morphine in and intramuscular buprenorphine 0.004 mg/kg. Single dose</td>
<td>Pain, Respiratory depression, Sedation, Nausea, Vomiting, Pruritus</td>
</tr>
</tbody>
</table>

IM, intramuscular; SEM, standard error of the mean; PCA, patient-controlled opioid analgesia.
various analgesics. Qualitatively, six studies found no difference between buprenorphine and morphine and three studies showed significantly less use of rescue analgesia in the buprenorphine group. Quantitatively, there was no difference in incidence of breakthrough analgesia requirement between buprenorphine and morphine (OR 0.81; 95% CI: 0.43 to 1.54; I²=0%; P=0.53; n=191; Figure 3).

Secondary outcomes

Eight studies (12-14,18,20-22,25) investigated respiratory depression via a variety of endpoints including incidence of respiratory depression [respiratory rate (RR) <10 breaths/min], PaCO₂ and mean RR. Six studies showed no difference and two showed an increased incidence of respiratory depression. Three studies with a total 220 patients had sufficient data for analysis (12,14,18). There was no difference in respiratory depression between groups (OR 4.07; 95% CI: 0.44 to 37.62; I²=0%; P=0.22).

Seven studies with a pool of investigated the incidence of sedation (12,18-21,23,24). There was no significant difference of sedation between buprenorphine and morphine (OR 1.77; 95% CI: 0.38 to 8.34; I²=59%; P=0.47; n=280).

Eight studies with a combined investigated the incidence of post-operative nausea (12-14,18,21-25), in which there was no difference between buprenorphine and morphine (OR 1.05; 95% CI: 0.62 to 1.76; I²=0%; P=0.86; n=442). Similarly, no difference was found in postoperative vomiting in an analysis of six studies (OR 0.99; 95% CI: 0.47 to 2.09; I²=18%; P=0.98; n=330) (12,14,18,22-24). Three studies examined and found no difference in postoperative dizziness (12,19,23). Six out of 7 studies showed no difference in the incidence of postoperative hypotension (12-14,20,22,23,25).

Discussion

This is the first systematic review and meta-analysis...
likely to experience euphoria and withdrawal with its use (6,33,34). Subsequently, risk of addiction is reduced with buprenorphine and patient drug seeking is significantly limited (9,10). It follows that buprenorphine’s use in the postoperative setting could play a vital preventative role in efforts to contain opioid abuse.

It should also be remembered that with buprenorphine’s antagonism of kappa receptors, patient dysphoria—a troublesome side effect of opioids—is unlikely with its use (26).

This study was limited by the lack of evidence for the potential secondary benefits of buprenorphine in the immediate postoperative period. Firstly, abdominal surgery frequently induces a delay in gastric emptying and the urge remain recumbent. This impairs opioid absorption and may render pharmacokinetics unpredictable (35,36). Furthermore, postoperative patients are not uncommonly on complete bowel rest for a short period as a result of intolerance to per oral fluids and solids. This often necessitates pro re nata IM, IV or subcutaneous opioid administration, regularly in the form of PCA. Such equipment is bulky and inconvenient for patient mobilization. More flexible routes of administration and an extended half-life mean buprenorphine has the potential to limit the duration of or completely circumvent the need for PCA. The hypothetical improvements to patient mobility could shorten ileus duration as well as prevent many pulmonary, frailty and pressure area complications (37-40). Given sublingually, buprenorphine may also expedite the removal of intravenous lines and their infection risks (11). Such potential benefits need further study if the true capabilities of the drug are to be elicted.

Our paper is hindered by a limited patient cohort, most of which was studied over 30 years ago. Necessarily, there is a lack of evidence in laparoscopic or robotic surgery. The term abdominal surgery encompasses a large array of operations and our study examines a varied population as a consequence. The intervention and control groups of the included studies differed in their route of administration and this must be considered when examining our outcomes. Each of the papers had incomplete outcome data. Multiple studies did not specify whether patients or assessors were blinded to the allocated intervention.

**Conclusions**

Buprenorphine is equivalent to morphine in managing pain after abdominal surgery. Buprenorphine has many possible but as to yet unproven benefits in this setting, including
eliminating the risk of opioid addiction and improving mobility. Respiratory depression appears to be unaltered when using buprenorphine or morphine. Without an effective antidote, buprenorphine may pose increased risk to patients with limited respiratory reserve.

Acknowledgments
None.

Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References


