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Original Contribution

Sublingual buprenorphine versus intravenous or intramuscular morphine in acute pain: A systematic review and meta-analysis of randomized control trials

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ABSTRACT

Intro: Buprenorphine is a potent analgesic agent w[illegible]eral unique and favourable features such as its sublingual formulation. The aim of this [illegible] to compare th[illegible]ctiveness of sublingual versus intramuscular and intravenous buprenorphine in a[illegible] pain.

Methods: Five major databas[illegible]ere systematically searched until April 2018. All randomized control trials comparing sublingual buprenor[illegible]e with intrav[illegible]us or intramuscular morphine in acute pain were included in this review. These studies w[illegible]assessed fo[illegible]el of evidence and risk of bias. The data was then analyzed both qualitatively and where a[illegible]riate b[illegible]eta-analysis. The primary outcomes were analgesic effect up to six hours and rescue analgesia req[illegible]he secondary outcomes were incidence of respiratory depression, nausea, vomiti[illegible] and hypotension.

Results: Nine stud[illegible] com[illegible]lingual and intramuscular or intravenous buprenorphine were identified and included 826 pati[illegible] The[illegible] difference in pain at any time point before six hours or need for rescue analgesia between t[illegible]gents. There was no difference in secondary outcomes between the two agents.

Discu[illegible] ublingua[illegible]renorphine offers an effective alternative to intravenous or intramuscular analgesia in ac[illegible]pain. [illegible]lingual b[illegible]enorphine appears to be a viable option in patients where intravenous access is difficult or not [illegible]urable.

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1. Introduction

The United States is [illegible]rentl[illegible]periencing an opioid overdose epidemic with a stro[illegible]orrela[illegible]n betw[illegible]en opioid prescribing and overdose related deaths [illegible]t Emer[illegible]cy Department (ED) literature has provided [illegible]ong fo[illegible]n th[illegible]e of non-opioid analgesic options [2]. A rec[illegible]st[illegible]by Jeffe[illegible]Colleagues (2018) showed that opioid pres[illegible]ng to [illegible]e patients from the ED carries a lower risk of longer-te[illegible]pioid [illegible]other acute settings [3]. Nonetheless improvemen[illegible]id prescribing in ED can undoubtedly be obtained.

Acute pain [illegible]ing opioid analgesia is common in the ED and a considered choice [illegible]iate agent is warranted. For example, agents such as oxycodone and hydromorphone have been linked with an increased propensity for the development of long-term addiction [4].

In recent years there has been a shift in the understanding of the clinical effect of buprenorphine. Buprenorphine is well known for its utility in the management of opioid use disorders (OUDs), however many recent studies have demonstrated its efficacy in the setting of acute pain management [5]. Buprenorphine possess a number of benefits including is analgesic benefits, agonist-antagonist pharmacodynamics which antagonizes the reward pathway and its somewhat unique formulations [6].

Buprenorphine is available in a number of formulations, including sublingual (SL). SL formulations have a number of practical benefits. Patients in whom intravenous (IV) access are difficult to obtain, in bowel obstructions where oral opioids are contraindicated, where IV lines are being minimized or in palliative care may benefit from SL formulations of analgesia. The purpose of this systematic review and meta-analysis is to compare the analgesic efficacy and time of onset of SL versus IV or intramuscular (IM) buprenorphine.

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2. Methods

2.1. Search strategy

Medline, Cochrane trials registry, SCOPUS, CINAHL and Web of Science were systematically searched from the inception of the databases until April 2018. This search was conducted by two independent reviewers (LW & RV) searching the terms (1) 'buprenorphine' AND 'acute pain'; (2) 'buprenorphine' AND 'Emergency Department' (3) 'buprenorphine' AND 'post-operative pain'. A manual reference check and citation check of included papers was performed via Google Scholar to identify any additional studies.

2.2. Study eligibility

Included studies were required to report on the use of sublingual buprenorphine versus IV or IM morphine in the management of acute pain in the ED or inpatient hospital setting. Studies investigating the use of buprenorphine in those with pre-existing chronic pain or on opioid substitution programs were excluded. Animal studies and non-clinical studies were excluded. Only randomized controlled trials (RCTs) were eligible for inclusion and there were no language criteria for exclusion. Two reviewers (LW and RV) independently assessed each study for inclusion in this systematic review.

2.3. Data extraction

The data from each article was independently extracted by two reviewers (LW and GA). 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.

2.4. Clinical outcome measures

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

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

Each article was evaluated using the criteria for Evidence Based Medicine (CEBM): Levels of Evidence Introductory Document [7]. These studies were then assessed for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias [8]. The results from each study were then grouped into individual outcomes. Due to the anticipated inconsistencies in outcome reporting measures both qualitative and quantitative analyses were performed. The qualitative analysis was conducted by grouping outcomes and then assigning a level of evidence ranking based on the collective strength of evidence [7].

1) Strong Evidence: Two or more high quality (quality score ≥4) randomized controlled trials (RCT) with ≥75% consistency in findings.
2) Moderate Evidence: One high quality RCT and two or more low quality studies with ≥75% consistency in findings.
3) Limited Evidence: One high quality RCT or multiple low quality studies with ≥75% consistency in findings.
4) Conflicting Evidence: Multiple low and/or high quality studies with ≤75% consistency in findings.
5) No Evidence: No studies could be found, may include technique reports

2.6. Statistical analyses

The combined data was analyzed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark), using the odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes, and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The Mantel-Haenszel (M-H) random effects model was used. Heterogeneity was assess 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.

2.7. Reporting

This study was reported in line with PRISMA guidelines [9].

3. Results

3.1. Literature search results

The initial systematic literature search yielded 2365 citations and a further 15 citations were identified through a manual citation and reference search of relevant articles [10-18]. Following the removal of duplicates, animal studies, review articles and non-clinical studies, 380 citations remained. These citations were screened based on title. Of these, 90 abstracts were screened and 55 full texts were retrieved for review. Nine articles met the inclusion criteria (Fig. 1) [10-18]. These nine studies included 826 patients (Table 1). Each study was then screened for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias (Fig. 2). Four studies met the criteria for high quality RCTs, the remaining five studies were of low quality.

3.2. Primary outcomes

Pain was measured using a variety of endpoints including various pain scores and at various time intervals. Eight studies used pain as an end point (Fig. 3). The data was analyzed in four time groups, namely at less than 1 h, 1 h, 3 h and 6 h. Qualitatively there was no difference in pain between patients who had received SL buprenorphine compared to morphine within the first hour. Quantitative analysis was performed using Visual Analogue Scale (VAS). At 1 h there was no difference in pain between the two

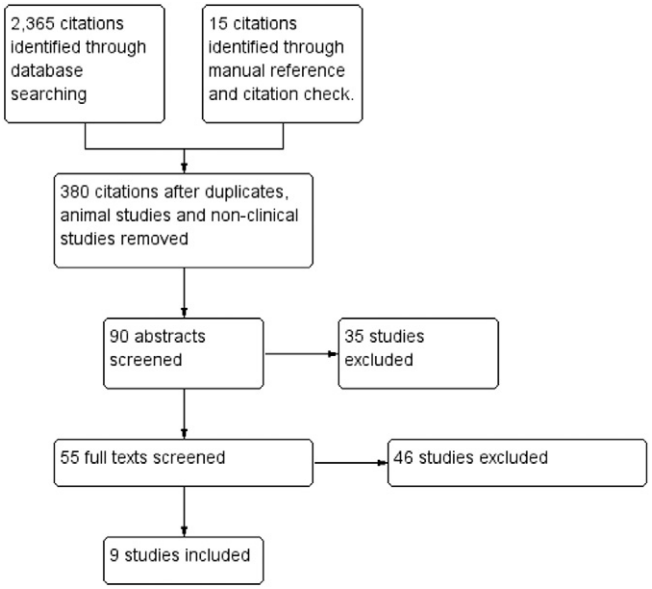

Fig. 1. Literature search.

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Table 1
Study characteristics.

Study	No pts. (buprenorphine: morphine)	Mean age (buprenorphine: morphine)	Mean weight (buprenorphine: morphine) (kg unless stated otherwise)	Intervention	Setting	Outcomes
Cuschieri et al. [10]	39:41	58 ± 14: 52 ± 15	63 ± 13: 63 ± 10	Intramuscular morphine 10 mg versus buprenorphine 0.3 mg intramuscular followed by sublingual buprenorphine 0.4 mg. Repeated dosing.	Abdominal surgery	1. Pain 2. Respiratory depression 3. Sedation 4. Nausea 5. Vomiting
Edge et al. [11]	49:52	43.8 ± 12.63: 44.6 ± 15.41	67.1 ± 8.53: 65.7 ± 8.65	Sublingual buprenorphine 0.4 mg versus intramuscular morphine 10 mg. Single dose.	Major surgery	1. Pain 2. Respiratory depression 3. Nausea 4. Vomiting 5. Sedation
Ellis et al. [12]	35:36	Cholecystectomy 51.3 ± 4.3: 53.7 ± 3.5; Herniorrhaphy 51.7 ± 2.7: 54.7 ± 2.5	Cholecystectomy 64.3 ± 3.6: 66.9 ± 2.1; Herniorrhaphy 72.0 ± 2.1: 75.5 ± 2.3	Sublingual buprenorphine 0.4 m[illegible]sus intramuscular morphine 10 m[illegible] Repeat dosing.	Abdo[illegible] surgery	1. Pain 2. Sedation
Gaitini et al. [13]	26:26	Not stated	Not stated	Sublingual Buprenorph[illegible]0.4 mg versus[illegible]tomy 1 mg Morphine PCA[illegible]eat dos[illegible]		1. Pain 2. Hypotension 3. Respiratory depression
Hosseininejad et al. [14]	101:102	40.50 ± 13.50: 39.85 ± 13.66	Not stated	2 mg subling[illegible]l bup[illegible]ne versu[illegible] intraveno[illegible]orphine [illegible]kg. Si[illegible] dose.	Emergency Department: Renal Colic	1. Time to analgesia 2. Pruritus
Jalili et al. [15]	49:50	35 ± 13: 35 ± 13	Not stated	Bupr[illegible]0.4 mg subling[illegible]versus M[illegible]ne 3[illegible]travenous. Single dose.	Emergency Department: Acute Pain	1. Pain 2. Nausea 3. Dizziness 4. Hypotension 5. Respiratory depression
Payandemehr et al. [16]	37:32	35 ± 10: 31 ± 10	Not stated.	Sublingual[illegible]prenorphine 2 mg versus Intraveno[illegible]orphine 0.1 mg/kg. Single dose.	ED Renal Colic	1. Pain 2. Nausea 3. Vomiting 4. Dizziness 5. Hypotension 6. Respiratory depression 7. Pruritus 8. Sedation 9. Rescue analgesia
Soltani et al. [17]	45:45	39.7 ± 18.0:35.8 ± 15.2[illegible]ted.		Sublingual buprenorphine 4.5 μg/kg vs intravenous morphine 0.2 mg/kg. Single dose.	Closed reduction orthopaedic surgery	1. Pain 2. Pruritus 3. Nausea 4. Vomiting 5. Hypotension
Weiss & Ritz [18]	30:31	Not stated[illegible]t stated.		Sublingual buprenorphine 4.5 μg/kg vs intravenous morphine 0.2 mg/kg. Single dose.	Emergency Department: Acute Myocardial Infarction	1. Pain 2. Respiratory depression 3. Nausea 4. Vomiting

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patient groups (WMD = 0.[illegible]95% CI = −0.32–1.05; I^2 = 94%; P = 0.30). At 3 h two high quality [illegible]ies sh[illegible]d significant improvement in pain using buprenorphine a[illegible]os[illegible]o morp[illegible]e (WMD 0.36; 95% CI = −0.32–1.05; I^2 = 93%; P < 0[illegible] At 6 h t[illegible]high quality studies reported pain was signific[illegible]approve[illegible]h [illegible]renorphine compared to morphine (WMD [illegible]1.3[illegible]5% CI = [illegible]o to −0.68; I^2 = 94%; P = 0.008).

3.3. Secondary outcomes

3.3.1. Respiratory depression

Six studies investigated respiratory depression via a variety of endpoints including incidence of respiratory depression (RR < 10), PaCO2 and mean respiratory rate. Of these three were high quality and three were low quality studies. Quantitative analysis showed no difference between sublingual buprenorphine and morphine (WMD = 0.81; 95% CI = 0.31–2.17; I^2 = 0; P = 0.38) (Fig. 4).

Four studies investigated the incidence of vomiting. No difference was found in incidence of vomiting between patients receiving sublingual buprenorphine or morphine (WMD 0.95; 95% CI = 0.48–1.89; I^2 = 0%; P = 0.89) (Fig. 5). Five studies found no difference in the incidence of nausea between buprenorphine and morphine (WMD 0.86; 95% CI = 0.55–1.35; I^2 = 0%; P = 0.52) (Fig. 6).

3.3.2. Hypotension

Four studies investigated the incidence of hypotension. Three were high quality studies and one was a low quality study. Quantitative analysis showed no difference between the two agents (WMD = 0.49; 95% CI = 0.10–2.34; P = 0.37) (Fig. 7).

3.3.3. Dizziness

Two high quality papers reported the incidence of dizziness and found no difference (WMD = 1.29; 95% CI = 0.29–5.78; I^2 = 77%; P = 0.74) (Fig. 8).

3.3.4. Rescue analgesia and time to first analgesia

One study reported on time to first analgesia and demonstrated no difference between the two agents [14]. One study reported on rescue

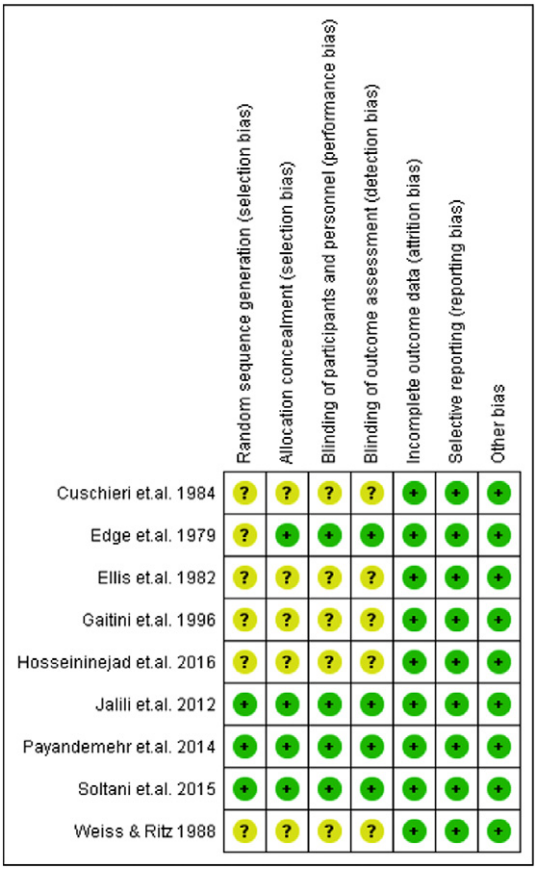

Fig. 2. Risk of bias summary.

analgesia and reported no difference in the incidence of rescue [illegible] use (WMD = 2.34; 95% CI = 0.42–13.01; P = 0.33) [16].

3.3.5. Subgroup analysis: low dose sublingual buprenorphine versus IV/IM morphine

Two studies reported using 2 mg SL buprenorphine and seven studies reported lower doses. Subgroup analysis of lower dose buprenorphine was performed.

Pain as measured by VAS was assessed for lower dose buprenorphine only. At less than 1 hour difference was noted in pain (WMD = −0.04; 95% CI = −0.70–0.70; P = 0.92). Pain measured at one to six hours post administration found no difference, with the confidence interval crossing the null value (WMD = −0.95; 95% CI = −1.92–0.02; I² = 99%; P = 0.02). No significant differences were noted in incidence of respiratory depression (OR = 1.67; 95% CI = 0.20–13.89; I² = 0%; P = 0.63) or vomiting (OR = 0.91; 95% CI = 0.42–1.94; I² = 0%; P = 0.83).

There was insufficient data available to assess differences between hypotension, dizziness, nausea, pruritis and time to first rescue analgesia. There was insufficient data to group perform a subgroup analysis of the studies examining the use of 2 mg SL buprenorphine.

4. Discussion

This is the first systematic review to compare the clinical effectiveness of sublingual buprenorphine with intravenous or intramuscular morphine in the setting of acute pain management. Nine RCTs with 826 patients were included in this review. Included in this review were four ED studies and five post-surgery studies. Our review was in keeping recent studies, which showed that buprenorphine has similar analgesic and adverse effect properties as intravenous or intramuscular morphine [5,19].

Alongside methadone, buprenorphine is most well known for its role in the management of OUD [20]. Under certain circumstances buprenorphine is known to be the safer of the two agents in treating opioid dependence [20]. This was initially thought to be due to its partial agonist-antagonist activity, which was also the reason why buprenorphine has been relatively under-utilized in the setting of acute pain. It is now well known that buprenorphine is approximately 33 times more potent than morphine, with no clinically observable ceiling effect in regards to analgesia [19,21]. The present study demonstrates an interesting analgesic profile in contrast to well-validated pharmacokinetic studies [22]. Sublingual buprenorphine produced a significant analgesic effect, much faster than expected. Overall, sublingual buprenorphine produced equivalent analgesia to morphine at three time points within the first hour of dosing [11,15-17]. Beyond an hour buprenorphine due to its slower elimination kinetics produced a significantly greater analgesic effect than intravenous morphine [22]. Time to first analgesia was reported in one study, which demonstrated no difference between the SL buprenorphine and IV morphine in emergency department presentations of renal colic [14].

Ideal dosing buprenorphine in acute pain remains to be clarified. At 1 to 6 h, pain was significantly improved in the cohort that included the two studies utilizing 2 mg dosing. No difference was noted at 1 to 6 h between buprenorphine and morphine when these two studies were excluded in subgroup analysis. Subgroup analysis of lower dose buprenorphine investigated the incidence of respiratory depression and vomiting and no difference compared to IM or IV morphine. Insufficient data was available to determine the association with other adverse effects. The 2 mg dose of buprenorphine may therefore provide better analgesia, in keeping with its proposed lack of clinical ceiling effect for analgesia. However, the adverse effect profiles of higher dose versus lower dose sublingual buprenorphine relative to morphine cannot be adequately described based on current available literature. This would be an important factor to assess in any future research.

It is worth noting that buprenorphine displayed a similar clinical adverse effect profile to morphine in regard to respiratory depression, sedation, hypotension, nausea and vomiting. This is contrary to well-publicized data showing a ceiling effect on respiratory depression and sedation [19]. This variation is likely related to the multimodal analgesic strategies implemented in most emergency departments as well as a much more diverse sample population, which include elderly patients with multiple comorbidities. Therefore, caution is advised when using buprenorphine in the acute setting.

In addition to the outcomes investigated in this review there are several well-documented advantages of sublingual buprenorphine. This includes the well-described kappa antagonism, which has been linked to both euphoric and dysphoric side effect [21]. This is an important consideration when using opioids in patients at high risk of developing an opioid addiction [1]. Furthermore, buprenorphine's non-renal metabolism makes it a safe long acting alternative in the setting of renal failure.

There are several limitations to this review including the small cohort of patients and the diversity of settings and study populations. There was also a lack of homogeneity in regard to the tools used to measure certain outcomes such as analgesic effect and respiratory depression. It is also worth noting that the majority of studies were underpowered to adequately detect the incidence of most adverse outcomes.

5. Conclusion

In conclusion, sublingual buprenorphine is an effective alternative to intravenous or intramuscular morphine in adult patients with acute pain. Sublingual buprenorphine appears to be of greatest benefit in patients in whom intravenous (IV) access is difficult to obtain, in bowel obstructions where oral opioids are contraindicated or where IV lines are being minimized. Ideal dosing of sublingual buprenorphine remains to be clarified and is an important area of future research. Caution is advised given that buprenorphine displays the same clinical adverse effect profile as other opioids in regards to the risk of respiratory depression and sedation.

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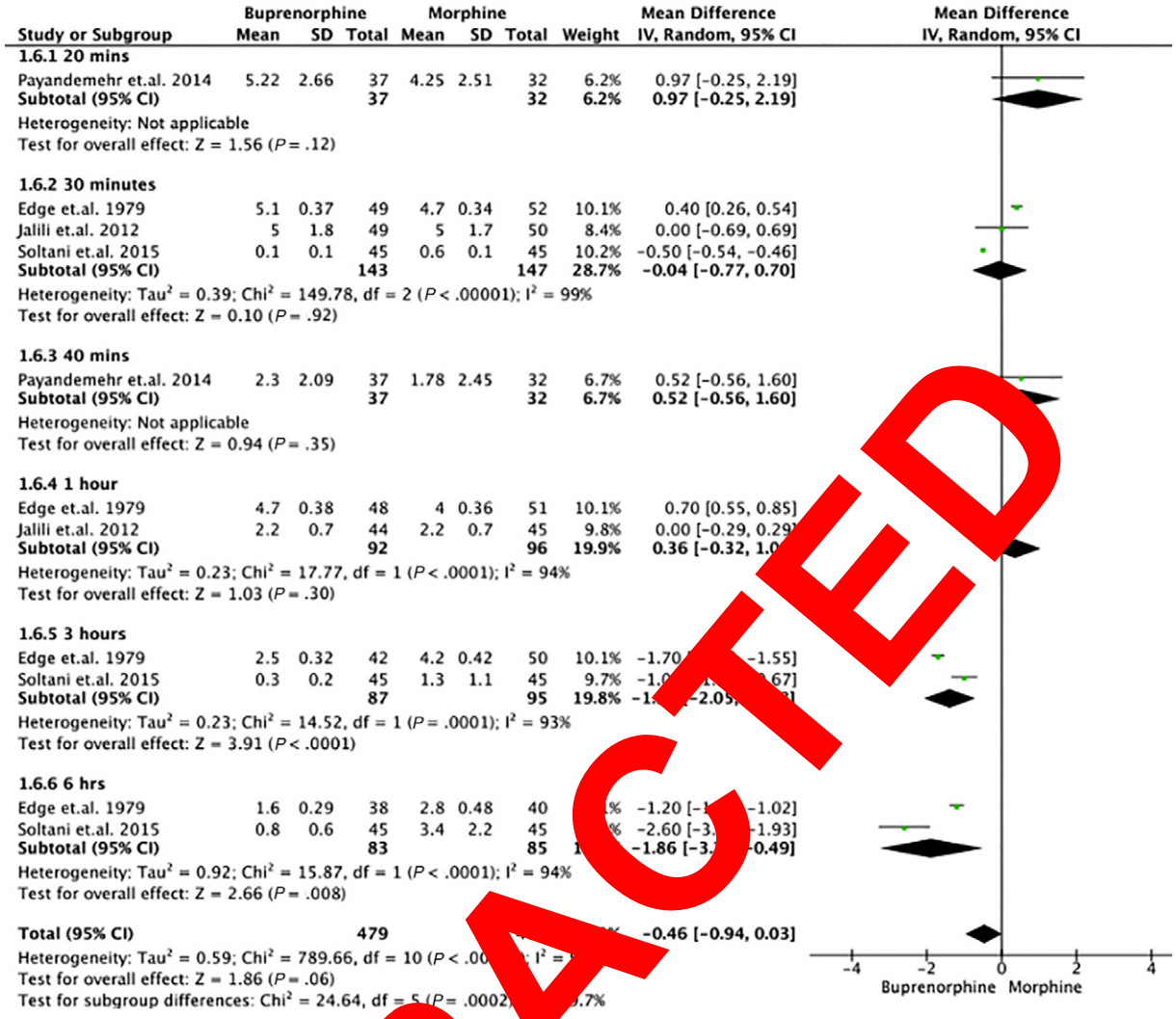

Fig. 3. Pain.

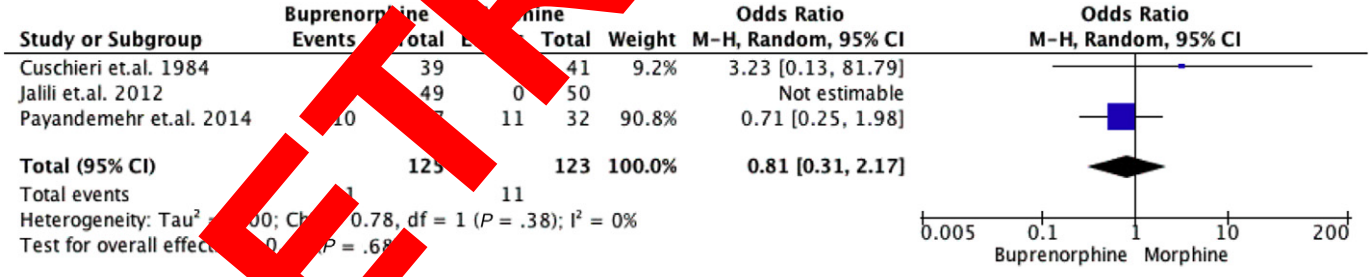

Fig. 4. Respiratory depression.

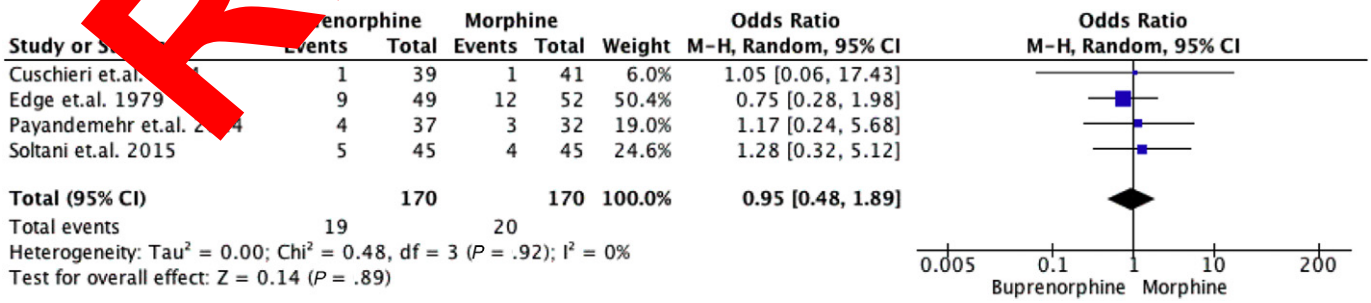

Fig. 5. Vomiting.

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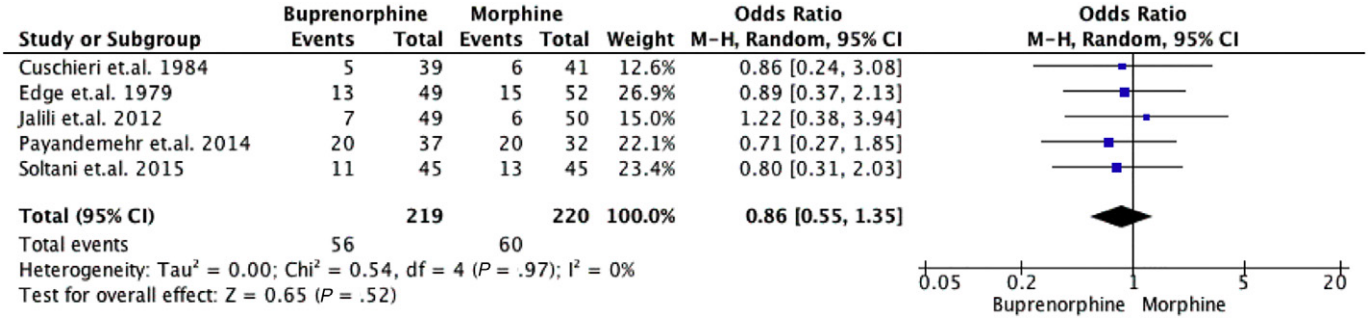


Fig. 6. Nausea.

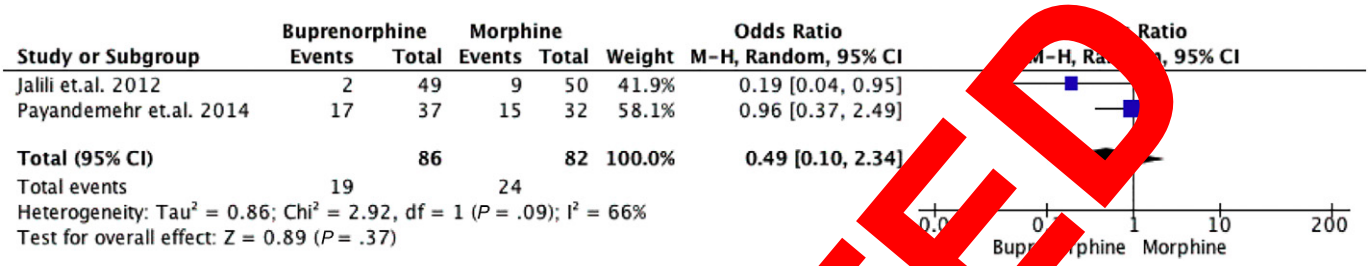
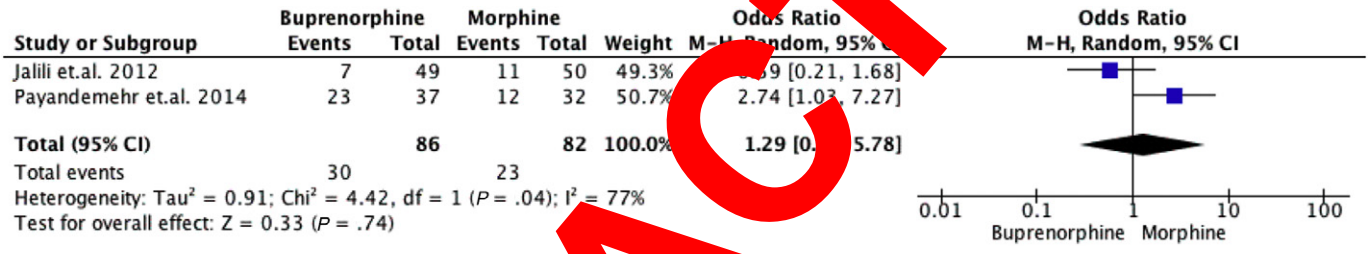


Fig. 7. Hypotension.



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