Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 643–651 doi:10.1111/j.1365-2044.2008.05817.x

REVIEW ARTICLE

Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis

M. Gehling[1] and M. Tryba[2]

1 Consultant Anaesthetist and 2 Head of Department, Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, Klinikum Kassel, Kassel, Germany

Summary

Intrathecal morphine is often used for postoperative analgesia after surgery. We performed a meta-analysis to obtain more detailed information on the frequency of side-effects in patients receiving intrathecal morphine in combination with spinal anaesthesia compared with placebo treated patients. We clustered the analysis to patients receiving placebo, less than morphine 0.3 mg ($M < 0.3$), or equal to or more than morphine 0.3 mg ($M \geq 0.3$) and calculated the risk ratios of morphine vs placebo. Twenty-eight studies investigating 46 morphine groups vs placebo were included. A total of 790 patients with intrathecal morphine and 524 patients who received placebo were analysed. Compared with placebo the lower dose of morphine resulted in an increase of nausea (RR 1.4, 95% CI 1.1–1.7), vomiting (RR 3.1, 95% CI 1.5–6.4) and pruritus (RR 1.8, 95% CI 1.4–2.2). The higher dose resulted in an increased risk ratio for pruritus (RR 5.0, 95% CI 2.9–8.6), but not nausea (RR 1.2, 95% CI 0.9–1.6) or vomiting (RR 1.3, 95% CI 0.9–1.9). Overall, intrathecal morphine did not increase respiratory depression. However, the higher dose of intrathecal morphine was associated with more episodes of respiratory depression (7/80) compared with the lower dose (2/247). Intrathecal morphine is associated with a mild increase in side-effects. With a dose < 0.3 mg we found there were no more episodes of respiratory depression than in placebo patients who received systemic opioid analgesia.

Correspondence to: Dr Markus Gehling
E-mail: gehling@klinikum-kassel.de
Accepted: 11 November 2008

Since 1979 intrathecal morphine has been used for postoperative pain management [1]. Effective analgesia can be obtained with doses ranging from 0.1 to 2.5 mg [2–7]. In recent years low doses of intrathecal morphine ranging from 0.1 to 0.25 mg have bene used to reduce side-effects and complications. Low-dose intrathecal morphine in combination with spinal anaesthesia has provided effective and safe analgesia for Caesarean section [8], haemorrhoidectomy [9], tubal ligation [10], transurethral prostatectomy [11], gynaecological surgery [12], and orthopaedic surgery [2].

The risks and side-effects of intrathecal morphine include nausea, vomiting, pruritus, urinary retention or respiratory depression. Gwirtz and colleagues reported a series of 5969 patients who received intrathecal morphine for postoperative analgesia [13]. They observed an incidence of respiratory depression of 3% in their patients. However, representative data on the incidence of side-effects and complications in patients receiving intrathecal morphine compared with placebo are lacking. We conducted a meta-analysis of randomised controlled studies investigating intrathecal morphine for postoperative analgesia. The aim of our study was to calculate the risk ratio of side-effects and complications in relation to placebo treated patients. Only reports of intrathecal morphine in combination with spinal anaesthesia were included, as general anaesthesia is associated with a different side-effect profile and intrathecal morphine doses combined with general anaesthesia are often higher than when combined with spinal anaesthesia.

Methods

Randomised, controlled studies were extracted in a Medline®-search from 1966 to 2007. The search terms 'spinal' and 'morphine' and 'postoperative' were

combined in a free text search using Boolean logic. In addition, we extracted studies from the reference lists of publications identified in the Medline search. The authors were not contacted to provide unpublished data. Studies met inclusion criteria if they investigated intrathecal morphine for postoperative analgesia in a randomised, placebo-controlled trial. The restriction to placebo-controlled studies was necessary in order to calculate the risk ratio. However, patients in the placebo groups often received systemic opioids for postoperative analgesia. The quality of included reports was analysed according to recommendations described by McQuay and Moore [14]. The resulting method score was calculated from documented randomisation, blinding and withdrawals. The greater the method score the better the quality (reliability and validity) of the trial. In a subgroup analysis we calculated the outcome parameters for each method score.

Two independent authors extracted the relevant data from included studies. Data published more than once were included only once in the analysis. We documented the type of surgery, study design, dose of intrathecal morphine and the local anaesthetic. The end-points of our study were the frequency of nausea, vomiting, pruritus, urinary retention and respiratory depression. The frequency of nausea, emesis or pruritus was calculated from the number of patients reporting any problem. Urinary retention was recorded if a urinary catheter had to be placed because of urinary retention or any other problem. Patients at risk for respiratory depression were extracted from data on the frequency of respiratory rate of less than either 12, 10 or 8 breaths.min^{-1}. All studies used one of these definitions of respiratory depression.

We calculated the relative risk for nausea, vomiting, pruritus and urinary retention. The relative risk of respiratory depression could not be calculated because the control event rate (CER) was zero and the calculation would result in a division by 0. Therefore, we computed the risk difference between placebo and morphine for this parameter. We calculated the risk as incidence divided by the number of included patients. The difference between the risks of morphine and placebo equals the risk difference (RD). A risk difference of 0 demonstrates equal risk in both groups. A negative (< 0) RD favours morphine (intrathecal morphine), whereas a positive (> 0) RD means a reduced risk in the placebo group.

We used the fixed effects model and analysed heterogeneity with Cochrane's Q and I^2 tests as a measure of inconsistency of study results. Increased heterogeneity indicates the risk of misinterpretation due to differences in study design. The forest plot gives an idea of the extent of heterogeneity showing the effect size and 95% confidence interval (CI) for each study. Cochrane's Q is a statistical measure of heterogeneity derived from the weighted sum of squared differences between individual study effects and the pooled effect across studies. As a more intuitive parameter of heterogeneity I^2 describes the relation between the difference of Q minus the degree of freedom and Q. It gives a result expressed in percentage of variation related to heterogeneity and not chance. All analytical procedures were conducted with the statistical program COMPREHENSIVE META ANALYSIS V2 (Biostat^{TM}, Englewood, USA).

Results

The trial flow is presented in Fig. 1. Twenty eight publications were included in the final analysis (see Table 1). Six studies had a method score of 5, six had a score of 4, 13 trials had a score of 3 and three trials had a score of 2. We found no significant heterogeneity within the analysed subgroups for nausea, vomiting, pruritus, urinary retention or respiratory depression. Data from 790 patients receiving intrathecal morphine and 524 placebo patients were analysed. The documented data on side-effects and complications differ between studies considerably. Thus, there are differences in the number of studies with useful data depending on the analysed side-effect.

The incidence of nausea was documented in 24 studies. Since some of the studies investigated different doses of morphine a total number of 41 study groups were

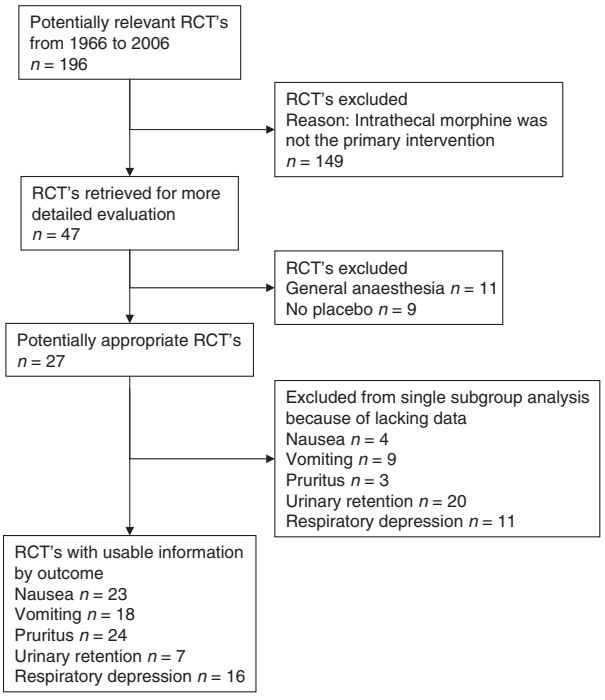

Figure 1 Trial flow chart.

Table 1 Descriptive data of included studies.

Lead author	Year of publication	Ref	Type of surgery	Study design	Dose of morphine (mg)	Number in morphine group	Number in placebo group	Method score
Abboud	1988	[8]	Caesarean section	rdb	0.25	11	12	4
Abboud	1988	[8]	Caesarean section	rdb	0.1	10	12	4
Abouleish	1993	[15]	Caesarean section	rdb	0.2	20	21	4
Abouleish	1988	[16]	Caesarean section	rdb	0.2	17	17	4
Almeida	2003	[17]	Gynaecology	R	0.1	12	12	3
Amanor-Boadu	1992	[9]	Haemorrhoids	R	0.5	13	14	2
Campbell	2001	[10]	Tubal ligation	rdb	0.1	30	30	3
Chung	1998	[18]	Caesarean section	R	0.1	20	20	3
Cole	2000	[19]	Total knee replacement	rdb	0.3	18	18	5
Cunningham	1983	[11]	Transurethral prostatectomy	R	1	12	12	3
Drakeford	1991	[3]	Total hip replacement	rdb	0.5	65	64	3
Eichler	2004	[20]	Arthroscopy	rdb	0.1	20	20	5
Forgaty	1993	[21]	Total hip replacement	R	1	30	30	3
Gehling	2003	[22]	Total hip/knee replacement	rdb	0.1	15	15	5
Goyagi	1995	[12]	Gynaecology	R	0.2	13	12	2
Grace	1995	[23]	Total hip replacement	R	0.5	30	30	5
Habib	2005	[24]	Tubal ligation	rdb	0.05	28	29	3
Johnson	1992	[25]	Total hip replacement	rdb	0.3	10	10	3
Kalso(†)	1983	[2]	Orthopaedics	rdb	0.2	10	10	3
Kalso(*)	1983	[2]	Orthopaedics	rdb	0.4	10	10	3
Kalso(†)	1983	[2]	Orthopaedics	rdb	0.4	10	10	3
Lanz	1984	[26]	Orthopaedics	rdb	0.5	23	19	4
Mora	1985	[27]	Transurethral prostatectomy	R	0.5	15	15	3
Mora	1985	[27]	Transurethral prostatectomy	R	1	15	15	3
Murphy	2003	[28]	Total hip replacement	rdb	0.05	15	15	5
Murphy	2003	[28]	Total hip replacement	rdb	0.1	15	15	5
Murphy	2003	[28]	Total hip replacement	rdb	0.2	15	15	5
Palmer	1999	[29]	Caesarean section	R	0.025	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.05	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.075	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.1	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.2	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.3	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.4	12	12	3
Palmer	1999	[29]	Caesarean section	R	0.5	12	12	3
Paterson	1984	[7]	Orthopaedics	R	0.625	21	10	3
Paterson	1984	[7]	Orthopaedics	R	1.25	17	10	3
Paterson	1984	[7]	Orthopaedics	R	2.5	14	10	3
Rathmell	2003	[30]	Orthopaedics	R	0.1	20	20	5
Rathmell	2003	[30]	Orthopaedics	R	0.2	20	20	5
Rathmell	2003	[30]	Orthopaedics	R	0.3	20	20	5
Sakai	2003	[31]	Transurethral prostatectomy	rdb	0.05	13	14	4
Sakai	2003	[31]	Transurethral prostatectomy	rdb	0.1	15	14	4
Schaer	1992	[32]	Orthopaedics, haemorrhoids	R	0.06–0.08	15	15	2
Sites	2003	[33]	Total knee replacement	rdb	0.25	20	21	4
Tan	2001	[34]	Total knee replacement	R	0.3	20	20	3

R = randomised study, rdb = randomised double blind trial, * = patients aged 30–50 years, † = patients aged 60–80 years.

analysed. We compared the results of 644 morphine and 431 placebo patients.

Nausea was documented in 28% of placebo patients. Overall, intrathecal morphine resulted in an increase in nausea with a RR = 1.3, 95% CI 1.1–1.5 (see Fig. 2). We did not find a dose–response relationship ($RR_{< 0.3\ mg}$ = 1.4, 95% CI 1.1–1.7 vs $RR_{\geq 0.3\ mg}$ = 1.2, 95% CI 0.92–1.55). Different doses were not associated with significant heterogeneity between the analysed studies (p = 0.508). We found an increased relative risk of nausea in studies with a method score of 4 ($RR_{method\ score\ =\ 4}$ = 3.4, 95% CI 1.7–6.6), but not in those with a method score of 5.

The incidence of vomiting was calculated from 19 trials with data from 504 morphine and 336 placebo patients. In the placebo patients 12% reported vomiting. Intrathecal morphine increased the risk of postoperative vomiting with a RR = 1.6, 95% CI 1.1–2.2 (see Fig. 3). However, lower doses of morphine (< 0.3 mg) resulted in an increased incidence of vomiting compared with studies of

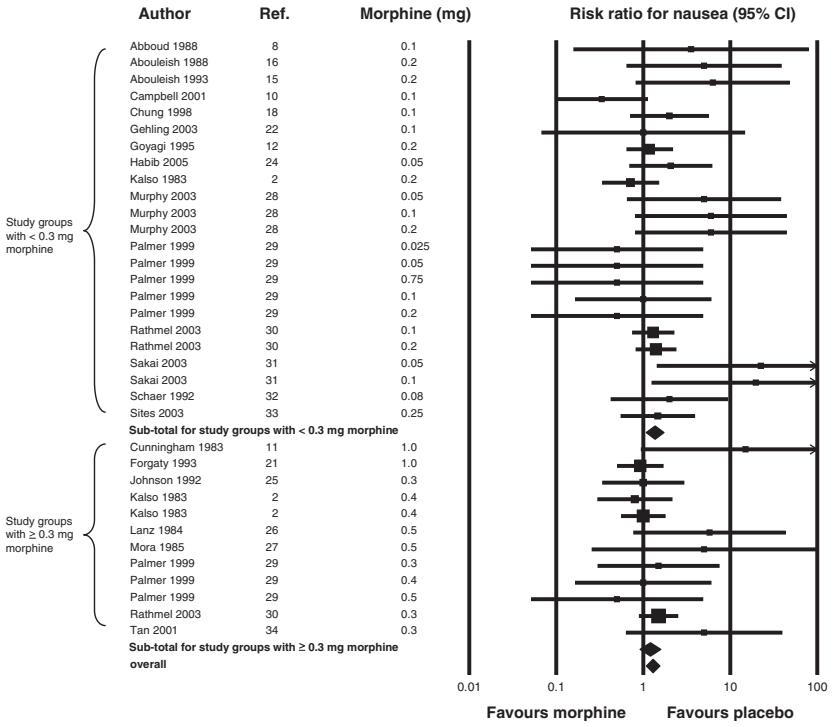

Figure 2 Risk of nausea after intrathecal morphine.

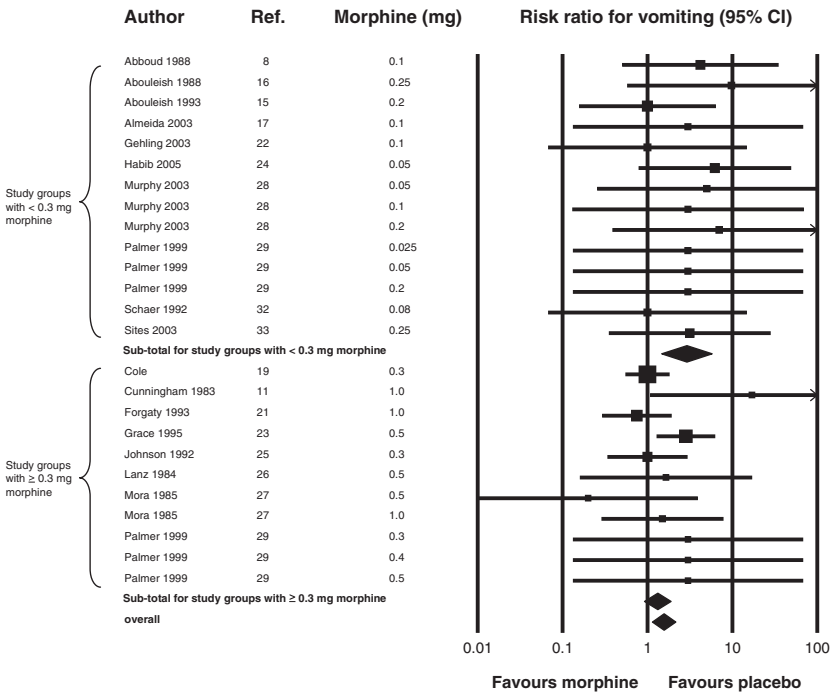

Figure 3 Risk of vomiting after intrathecal morphine.

morphine ≥ 0.3 mg ($RR_{< 0.3\ mg}$ = 3.1, 95% CI 1.5–6.4 vs $RR_{\geq 0.3\ mg}$ = 1.3, 95% CI 0.9–1.9). This finding was not associated with an increased heterogeneity within the subgroups ($p_{< 0.3\ mg}$ = 0.988 and $p_{\geq 0.3\ mg}$ = 0.287). The point estimate for vomiting showed a trend for an increased relative risk in studies with a method score of 4 ($RR_{method\ score\ =\ 4}$ = 2.5, 95% CI 0.9–6.6), but not with a method score of 5.

Data of the incidence of pruritus were extracted from 25 studies including 700 morphine and 434 placebo patients.

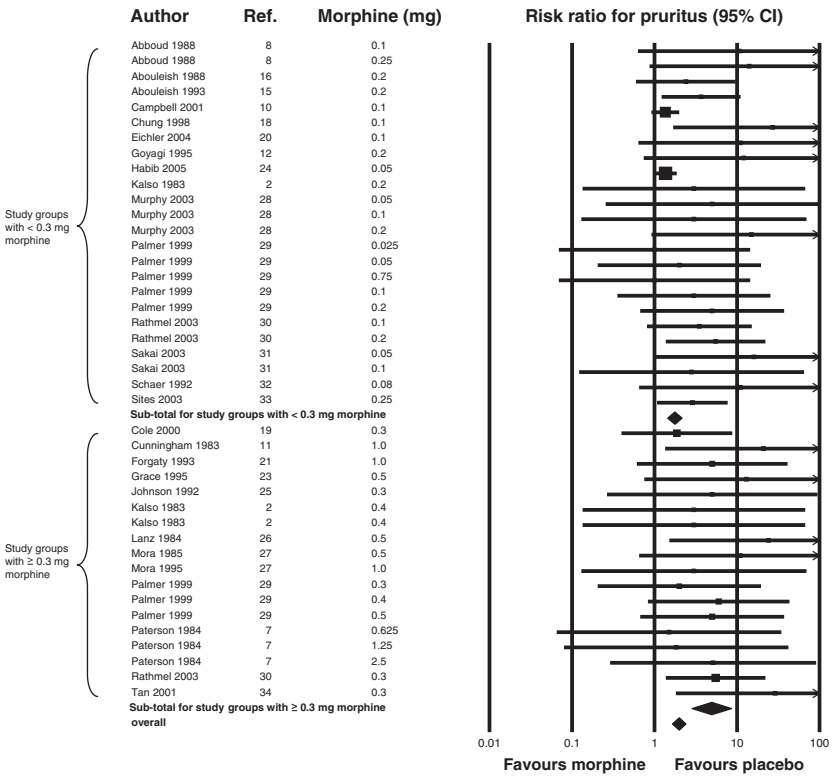

Figure 4 Risk of pruritus after intrathecal morphine.

Twelve percent of placebo patients and 37% of the patients in the morphine groups experienced pruritus. Intrathecal morphine was associated with an increased frequency of pruritus (RR = 2.0, 95% CI 1.6–1.2.4, see Fig. 4). Pruritus increased with dose of intrathecal morphine ($RR_{< 0.3\ mg}$ = 1.8, 95% CI 1.4–2.2 vs $RR_{\geq 0.3\ mg}$ = 5.0, 95% CI 2.9–8.6). We found no significant heterogeneity within the subgroups ($p_{< 0.3\ mg}$ = 0.120 and $p_{\geq 0.3\ mg}$ = 0.963). The relative risk increased with the method score ($RR_{method\ score\ =\ 3}$ = 1.6, 95% CI 1.3–2.0, $RR_{method\ score\ =\ 4}$ = 4.0, 95% CI 2.2–7.0 and $RR_{method\ score\ =\ 5}$ = 4.7, 95% CI 2.5–8.7). However the highest relative risk was calculated in two studies with a method score of 2 ($RR_{method\ score\ =\ 2}$ = 11.5, 95% CI 1.6–83.1).

Since urinary catheterisation was routinely performed in many trials, only eight could be analysed for urinary retention after intrathecal morphine. A total of 223 morphine and 177 placebo patients were included. Urinary retention was observed in 17% of placebo patients. Intrathecal morphine did not increase the risk of urinary retention (RR = 1.3, 95% CI 0.9–1.9, see Fig. 5). However, due to the low number of patients included in the meta-analysis, a β-type error cannot be excluded. We did not observe a difference between dosing groups ($RR_{< 0.3\ mg}$ = 1.2, 95% CI 0.5–2.8 vs $RR_{\geq 0.3\ mg}$ = 1.3, 95% CI 0.9–2.0). The relative risk of urinary retention was not associated with the method score of the studies.

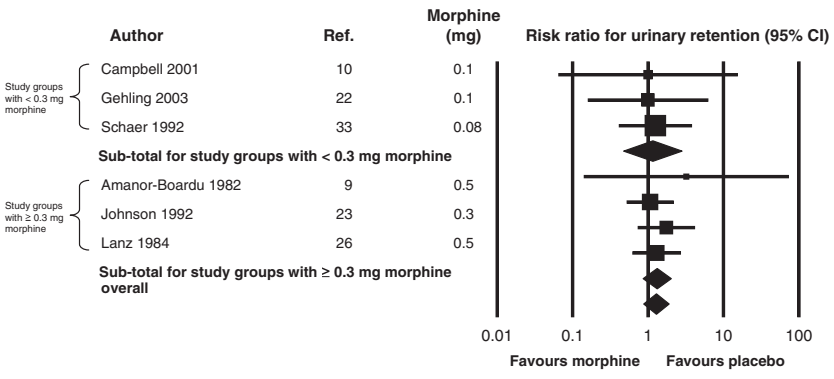

Figure 5 Risk of urinary retention after intrathecal morphine.

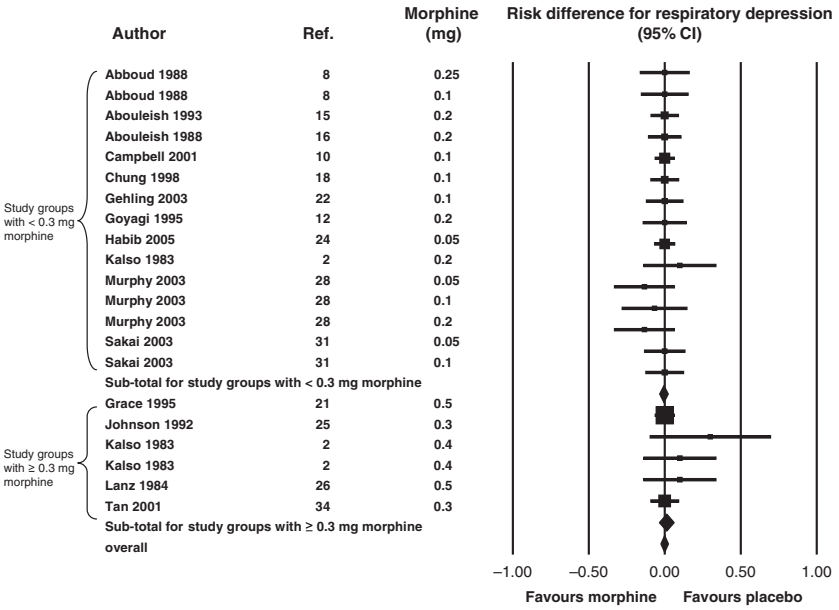

Figure 6 Risk of respiratory depression after intrathecal morphine.

The risk of respiratory depression was calculated from the number of patients with an observed episode of a respiratory frequency of less than 8 breaths.min^{-1} [10, 23, 24], 10 breaths.min^{-1} [8, 12, 15, 16, 18, 22, 31, 34] or 12 breaths.min^{-1} [2, 25, 28]. Data on the incidence of respiratory depression were available in 14 reports. In these trials the results of 327 morphine and 255 placebo patients were documented. In the placebo groups the rate of low respiratory frequency was 2%, whereas the rate in the morphine groups was 3%. In study groups with morphine < 0.3 mg the incidence was 2/247 (1%), whereas in those with morphine ≥ 0.3 mg it was 7/80 (9%). Intrathecal morphine did not have a significant influence on the risk of low respiratory frequency in our analysis (risk difference $RD_{< 0.3\ mg} = -0.005$, 95% CI -0.034 to 0.023 and $RD_{\geq 0.3\ mg} = 0.013$, 95% CI -0.036 to 0.062, see Fig. 6). However, due to the low number of patients in the morphine ≥ 0.3 mg subgroup, a β-type error cannot be excluded. The calculated risk difference of respiratory depression was not associated with the method score of the analysed studies.

Discussion

Case numbers in randomised controlled trials are primarily calculated for the investigation of efficacy, not to document risks of a treatment. Therefore, a meta-analysis may provide more precise information, especially on the risk of a specific treatment. In our analysis, patients receiving morphine < 0.3 mg in addition to spinal anaesthesia showed a significantly increased risk of nausea (RR = 1.4), vomiting (RR = 2.9), pruritus (RR = 1.8), and a slightly lower risk of respiratory depression compared with placebo patients treated with systemic opioids ($p > 0.05$). Patients receiving morphine ≥ 0.3 mg added to a spinal anaesthetic had a significant increase in the risk of pruritus (RR = 5.0), that was more marked than in patients receiving the lower dose of morphine. We found a trend to increased risks ratios for nausea, vomiting and urinary retention. Patients with morphine ≥ 0.3 mg also showed a trend to an increased rate of respiratory depression compared with placebo patients who also received postoperative analgesia via patient controlled analgesia (PCA). We found a trend towards a dose-dependent increase in risk of urinary retention and respiratory depression and an increase in the relative risk of pruritus in patients receiving larger doses of intrathecal morphine. The relative risk of nausea and vomiting, however, showed a trend to increase in patients receiving a lower morphine dose. Overall, intrathecal morphine was associated with an increased risk of nausea, vomiting, pruritus and urinary retention, although the number of analysed cases was insufficient for the calculation of a consistent dose-response relation. The risk of respiratory depression seems not to be increased in patients receiving morphine < 0.3 mg compared with placebo. Thus, respiratory depression can not be excluded in patients receiving intrathecal morphine or systemically administered opioids.

In our analysis we did not find a consistent relationship between the study results and the method score of the studies. This may be due to the exclusion of non-randomised and non placebo-controlled studies.

A meta-analysis and a review have looked at efficacy and side-effects of intrathecal opioids after Caesarean section or paediatric surgery [35, 36]. In patients

undergoing Caesarean section, the authors found clinically useful analgesia after intrathecal morphine, and, to a lesser extent, after fentanyl and sufentanil [35]. The combination of spinal anaesthesia and intrathecal morphine was associated with an increase in nausea, vomiting and pruritus. The incidence of nausea and vomiting was greater in patients who received intrathecal fentanyl than with morphine. In both groups, pruritus was observed with a similar frequency. In children, 0.002–0.025 mg.kg^{-1} morphine were administered via a single spinal injection for postoperative analgesia after spinal surgery [36]. Intrathecal morphine was associated with a longer duration of analgesia, decreased intravenous opioid requirements and reduced blood loss during surgery. Late respiratory depression occurred 6 h after surgery in five out of 33 patients [36]. Our analysis adds information on the risk ratio and provides a better understanding of the extent of these side-effects.

Intrathecal morphine results in a moderate and clinically relevant increase in nausea, vomiting, pruritus and urinary retention in our meta-analysis. Thus, prophylaxis for these side-effects seems to be mandatory if spinal anaesthesia is supplemented with intrathecal morphine. Clinical trials with intrathecal morphine showed a reduction in postoperative nausea and vomiting (PONV) in patients who received ondansetron 8 mg [37, 38], dexamethasone 8 mg [39] or haloperidol 1 mg [40] preoperatively. In the treatment of pruritus low doses of propofol (10 mg) were effective in two studies [41, 42], and the prophylactic administration of ondansetron reduced the risk of pruritus in one trial [43]. Unfortunately, we found no data in randomised controlled studies investigating prophylaxis or therapy for urinary retention after intrathecal morphine.

In our analysis, the risk ratio for vomiting was, paradoxically, increased among those patients who received a dose of intrathecal morphine less than 0.3 mg. Since these data are not associated with increased heterogeneity in the analysed subgroups, we have no explanation for this finding. Only two studies, however, directly compared intrathecal morphine in doses less than 0.3 mg with doses equal or more than 0.3 mg [2, 29], and we cannot exclude that the differences may be due to differences in the documentation of vomiting.

The most important risk after intrathecal morphine is of respiratory depression. As a marker for an increased risk of respiratory depression the frequency of patients with an episode respiratory rate of less than 8, 10 or 12 breaths.min^{-1} was documented. We found no increase in the risk of respiratory depression compared with placebo. However, almost all episodes of reduced respiratory frequency were observed in patients receiving morphine ≥ 0.3 mg [2, 11, 25]. The confidence interval demonstrates the chance of error in the calculated risk difference of respiratory depression. Due to the small number of cases our analysis does not have sufficient power to decide whether intrathecal morphine increases the risk of respiratory depression or not. However, changing from intrathecal to intravenous administration does not provide opioid analgesia without risk of respiratory depression. Patients in placebo groups who received systemic opioids via patient controlled analgesia (PCA) experienced episodes of low respiratory frequency in 2% of cases.

In a study of 5969 patients who received between 0.2 and 0.8 mg morphine intrathecally, Gwirtz and colleagues described the side-effects and complications of intrathecal morphine [13]. Without a control group they found nausea or vomiting in 25%, pruritus in 37% and respiratory depression in 3% of their patients [13]. Although the studies included in this meta-analysis used lower doses of intrathecal morphine, the results do not differ substantially from the data supplied by Gwirtz. High rates of observed side-effects may be due to the controlled study design we analysed. Recently, a retrospective analysis of the incidence of respiratory depression after intrathecal morphine 0.15 mg for Caesarean section has been published [44]. The authors found the incidence of an episode of respiratory rate ≤10 breaths.min^{-1} within 24 h of intrathecal morphine to be 0.26% and naloxone was needed by 0.052% of their patients. These results support the notion that lower doses of intrathecal morphine may be associated with a reduced risk of respiratory depression. However, there is no evidence that there is an effective dose of intrathecal morphine that is associated with no risk of respiratory depression.

Overall, the moderate incidence of side-effects seems to be justified by the quality and duration of analgesia provided by low dose intrathecal morphine added to a spinal anaesthesia. We conclude that intrathecal morphine for postoperative analgesia requires measures for prophylaxis and therapy of side-effects and continuous observation of the respiratory function of patients. The same is true, however, for patients who receive opioids systemically. There are no data to support the need for extended monitoring of patients who receive low dose intrathecal morphine.

References

1 Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *Anesthesiology* 1979; **50**: 149–51.
2 Kalso E. Effects of intrathecal morphine, injected with bupivacaine, on pain after orthopaedic surgery. *British Journal of Anaesthesia* 1983; **55**: 415–22.

3 Drakeford MK, Pettine KA, Brookshire L, Ebert F. Spinal narcotics for postoperative analgesia in total joint arthroplasty. A prospective study. *Journal of Bone and Joint Surgery (American volume)* 1991; **73**: 424–8.
4 Fogarty DJ, Milligan KR. Postoperative analgesia following total hip replacement: a comparison of intrathecal morphine and diamorphine. *Journal of the Royal Society of Medicine* 1995; **88**: 70–2.
5 Niemi L, Pitkanen MT, Tuominen M, Rosenberg PH. Comparison of intrathecal fentanyl infusion with intrathecal morphine infusion or bolus for postoperative pain relief after hip arthroplasty. *Anesthesia & Analgesia* 1993; **77**: 126–30.
6 Slappendel R, Weber EW, Dirksen R, Gielen MJ, van Limbeek J. Optimization of the dose of intrathecal morphine in total hip surgery: a dose-finding study. *Anesthesia & Analgesia* 1999; **88**: 822–6.
7 Paterson GMC, McQuay MHJ, Bullingham RES, Moore RA. Intradural morphine and diamorphine. *Anaesthesia* 1984; **39**: 113–17.
8 Abboud TK, Dror A, Mosaad P, et al. Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. *Anesthesia & Analgesia* 1988; **67**: 137–43.
9 Amanor-Boadu SD. Assessment of minidose intrathecal morphine for analgesia after hemorroidectomy. *West African Journal of Medicine* 1992; **11**: 146–9.
10 Campbell DC, Riben CM, Rooney ME, Crone LA, Yip RW. Intrathecal morphine for postpartum tubal ligation postoperative analgesia. *Anesthesia & Analgesia* 2001; **93**: 1006–11.
11 Cunningham AJ, McKenna JA, Skene DS. Single injection spinal anaesthesia with amethocaine and morphine for transurethral prostatectomy. *British Journal of Anaesthesia* 1983; **55**: 423–7.
12 Goyagi T, Nishikawa T. The addition of epinephrine enhances postoperative analgesia by intrathecal morphine. *Anesthesia & Analgesia* 1995; **81**: 508–13.
13 Gwirtz KH, Young JV, Byers RS, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain. *Anesthesia & Analgesia* 1999; **88**: 599–604.
14 McQuay HJ, Moore A. *An Evidence Based Resource for Pain Relief*. Oxford: Oxford University Press, 1998.
15 Abouleish E, Rawal N, Tobon-Randall B, et al. A clinical and laboratory study to compare the addition of 0.2 mg of morphine, 0.2 mg of epinephrine, or their combination to hyperbaric bupivacaine for spinal anesthesia in cesarean section. *Anesthesia & Analgesia* 1993; **77**: 457–62.
16 Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. *Anesthesia & Analgesia* 1988; **67**: 370–4.
17 Almeida RA, Lauretti GR, Mattos AL. Antinociceptive effect of low-dose intrathecal neostigmine combined with intrathecal morphine following gynecologic surgery. *Anesthesiology* 2003; **98**: 495–8.
18 Chung CJ, Kim JS, Park HS, Chin YJ. The efficacy of intrathecal neostigmine, intrathecal morphine, and their combination for post-cesarean section analgesia. *Anesthesia & Analgesia* 1998; **87**: 341–6.
19 Cole PJ, Craske DA, Wheatley RG. Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. *British Journal of Anaesthesia* 2000; **85**: 233–7.
20 Eichler F, Decker T, Muller E, Kasper SM, Rutt J, Grond S. [Efficacy and safety of 0.1 mg of intrathecal morphine in arthroscopic knee joint surgery]. *Der Schmerz* 2004; **18**: 515–19.
21 Fogarty DJ, Carabine UA, Milligan KR. Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. *British Journal of Anaesthesia* 1993; **71**: 661–4.
22 Gehling M, Tryba M, Lusebrink T, Zorn A. [Can the addition of clonidine improve the analgesic efficacy of low dose intrathecal morphine? A randomised double-blind trial]. *Der Anaesthesist* 2003; **52**: 204–9.
23 Grace D, Bunting H, Milligan KR, Fee JP. Postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement. *Anesthesia & Analgesia* 1995; **80**: 86–91.
24 Habib AS, Muir HA, White WD, Spahn TE, Olufolabi AJ, Breen TW. Intrathecal morphine for analgesia after postpartum bilateral tubal ligation. *Anesthesia & Analgesia* 2005; **100**: 239–43.
25 Johnson A, Bengtsson M, Soderlind K, Lofstrom JB. Influence of intrathecal morphine and naloxone intervention on postoperative ventilatory regulation in elderly patients. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 436–44.
26 Lanz E, Daublander M, Lipp M, Theiss D. 0.5 mg intrathecal morphine in spinal anesthesia. A double blind study on sensory block, postoperative analgesia and adverse effects. *Regional Anesthesia* 1984; **7**: 79–85.
27 Mora C, Dupuis JL, Feiss P. [Spinal anesthesia and morphine analgesia in prostatic surgery]. *Cahiers d'* Anesthesiologie 1985; **33**: 25–7.
28 Murphy PM, Stack D, Kinirons B, Laffey JG. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. *Anesthesia & Analgesia* 2003; **97**: 1709–15.
29 Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose-response relationship of intrathecal morphine for postcesarean analgesia. *Anesthesiology* 1999; **90**: 437–44.
30 Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. *Anesthesia & Analgesia* 2003; **97**: 1452–7.
31 Sakai T, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. *Canadian Journal of Anesthesia* 2003; **50**: 1027–30.
32 Schaer H, Baasch K, Prochacka K. [Intrathecal morphine for postoperative pain]. *Der Anaesthesist* 1992; **41**: 689–93.
33 Sites BD, Beach M, Biggs R, et al. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves

postoperative analgesia for total knee arthroplasty. *Anesthesia & Analgesia* 2003; **96**: 1083–8.
34 Tan PH, Chia YY, Lo Y, Liu K, Yang LC, Lee TH. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. *Canadian Journal of Anesthesia* 2001; **48**: 551–6.
35 Dahl JA, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects on intrathecal opioids in patientes undergoing cesarean section with spinal anesthesia. *Anesthesiology* 1999; **91**: 1919–27.
36 Tobias JD. A review of intrathecal and epidural analgesia after spinal surgery in children. *Anesthesia & Analgesia* 2004; **98**: 956–65.
37 Yazigi A, Chalhoub V, Madi-Jebara S, Haddad F, Hayek G. Prophylactic ondansetron is effective in the treatment of nausea and vomiting but not on pruritus after cesarean delivery with intrathecal sufentanil-morphine. *Journal of Clinical Anesthesia* 2002; **14**: 183–6.
38 Yazigi A, Chalhoub V, Madi-Jebara S, Haddad F. Ondansetron for prevention of intrathecal opioids-induced pruritus, nausea and vomiting after cesarean delivery. *Anesthesia & Analgesia* 2004; **98**: 264.
39 Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo. *British Journal of Anaesthesia* 2003; **90**: 665–70.
40 Parlow JL, Costache I, Avery N, Turner K. Single-dose haloperidol for the prophylaxis of postoperative nausea and vomiting after intrathecal morphine. *Anesthesia & Analgesia* 2004; **98**: 1072–6.
41 Saiah M, Borgeat A, Wilder-Smith OH, Rifat K, Suter PM. Epidural-morphine-induced pruritus: propofol versus naloxone. *Anesthesia & Analgesia* 1994; **78**: 1110–3.
42 Borgeat A, Wilder-Smith OH, Saiah M, Rifat K. Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76**: 510–2.
43 Yeh HM, Chen LK, Lin CJ, et al. Prophylactic intravenous ondansetron reduces the incidence of intrathecal morphine-induced pruritus in patients undergoing cesarean delivery. *Anesthesia & Analgesia* 2000; **91**: 172–5.
44 Kato K, Shimamoto H, Terui K, Yokota K, Miyao H. Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *Journal of Anesthesia* 2008; **22**: 112–16.