Definitions of "respiratory depression" with intrathecal morphine postoperative analgesia: a review of the literature

[Définitions de la "dépression respiratoire" de l'analgésie postopératoire réalisée avec de la morphine intrathécale : une revue documentaire]

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Purpose: To review the postoperative intrathecal morphine (ITM) analgesia literature for their definitions of "respiratory depression" (RD).

Source: Medline (1966 - June Week 5 2001) and reference lists were searched for original studies involving bolus-dose ITM for postoperative analgesia, which used "respiratory depression" or similar terms.

Principal findings: The search identified 209 studies. These were included if ITM use was appropriate (bolus dose, postoperative analgesia) and the term "respiratory depression" was used, which left 96 studies remaining. Forty-four (46%) did not define "RD" despite using this term. A further 24 (25%) defined RD with respiratory rate (RR) alone. Only 28 (29%) defined RD with more than RR alone. There was no statistically significant association between the presence of a definition for RD with study design, study size or publication period. Also, no significant association existed between rigorousness of RD definitions and the above factors.

Conclusion: The term "respiratory depression" has no clear definition from a review of the literature on ITM use for postoperative analgesia. While defining RD with bradypnea is superior to having no definition, this is still inadequate. In future research, the consistent use of terms with specific meanings will facilitate understanding the true incidence of ITM's respiratory effects. If "respiratory depression" is used, then an explicit definition of its meaning should be provided. Future research must also address what is clinically significant respiratory impairment from intrathecal opioids, and how to optimally monitor for this. Further delineating their risks *vs* benefits will allow for more optimal dosing.

Objectif : *Passer en revue les documents sur l'analgésie postopératoire, réalisée avec la morphine intrathécale (MIT), quant à leurs définitions de la "dépression respiratoire" (DR).*

Source : *La base Medline (1966 - Semaine 5, juin 2001) et les listes de lectures de référence ont été fouillées à la recherche d'études originales sur des bolus de MIT administrés comme analgésie postopératoire, et dans lesquelles on retrouve le terme "dépression respiratoire" ou des termes similaires.*

Constatations principales : *La recherche nous a fourni 209 études. Les études (96) comportant un usage approprié de la MIT (dose en bolus, analgésie postopératoire) et l'utilisation du terme "dépression respiratoire" ont été retenues. Malgré l'utilisation du terme "DR", 44 études (46 %) ne la définissaient pas. D'autres études, 24 (25 %), n'utilisaient que le terme "fréquence respiratoire" (FR) pour définir la DR. Seulement 28 (29 %) études en donnaient une définition plus large. Il n'y avait pas d'association significative entre la présence d'une définition de la DR et le devis de l'étude, sa taille ou sa date de publication. Aussi, aucune association significative n'a été trouvée entre la rigueur des définitions de la DR et les facteurs susmentionnés.*

Conclusion : *Le terme "dépression respiratoire" n'a pas de définition claire dans les documents examinés sur l'usage de la MIT comme analgésie postopératoire. Il est préférable de définir la DR par la bradypnée que de ne pas la définir, mais cela demeure incomplet. À l'avenir, l'usage uniforme de termes et de leurs définitions spécifiques facilitera la compréhension de la véritable incidence des effets respiratoires de la MIT. Le terme "dépression respiratoire" doit être accompagné d'une définition explicite. Les recherches à venir doivent traiter des affections respiratoires cliniques significatives causées par les opioïdes intrathécaux et de la façon de les déceler le plus efficacement. En déterminant davantage leurs risques et leurs bienfaits, nous pourrons en établir une posologie optimale.*

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SPINAL administrations of opioids offer segmental analgesia,[1] but have side effects including pruritus, nausea and vomiting, urinary retention, hypotension, and importantly, "respiratory depression" (RD), both early and delayed.[2–5]

Intrathecal morphine (ITM) was the opioid involved in many of the cases of delayed RD,[6–8] a serious but rare complication. ITM produces a dose-related analgesia and RD[2–4,9–14] via separate receptor mechanisms.[15] Peak RD with ITM occurs between 3.5 to 12 hr postinjection.[3,4,8,9,11,16,17] Large surveys report the incidence of RD after ITM ranging from 0.03%[18] up to 7%.[7] Some believe ITM is underused for routine postoperative analgesia[19] due to the risk of delayed RD.

Despite its severity, the term "respiratory depression" was inconsistently defined amongst studies.[20] Quite commonly, there was no definition whatsoever, despite the use of this term.[21,22] Definitions of RD in postoperative ITM analgesia literature included: a low respiratory rate (RR),[23] high arterial PCO_2 values,[24] low oxyhemoglobin saturation with pulse oximetry (SpO_2),[25] increased level of sedation (LOS),[26] depressed ventilatory response to hypoxia and hypercarbia,[27] the need for naloxone treatment,[7] or a combination of these. However, the lack of a more specific or uniform definition of RD makes it difficult to ascertain its true incidence. Statistics gathered from large retrospective studies and surveys are also difficult to interpret due to under-reporting from recall bias.[7]

Our objective was to review the postoperative ITM analgesia literature and examine their definitions of RD.

Methods

Systematic search

Medline (1966 - June Week 5 2001) was searched by the primary author for original studies (no case reports or letters) involving bolus-dose ITM for postoperative analgesia, which used "respiratory depression" or similar terms. "RD" was in the context of central RD, not from other etiologies such as neuromuscular disease.

Different search strategies were employed to include studies with the following Medical Subject Headings (MeSHs) in the title or abstract: "injections, spinal", "anesthesia, spinal", and "morphine", along with key words in the title or abstract: "intrathecal morphine", "subarachnoid morphine", "spinal morphine", and "subdural morphine". Only studies involving adult humans published in English were included. Additional reports were found through reference list searches.

Studies were excluded with the following MeSHs: "neoplasms", "palliative care", "pain, intractable", "long-term care", "infusion pumps", "labour", "case report", "child", or "adolescent" and the following key words: "chronic pain", "cancer", "labour pain", or "labour". Unpublished trials and abstracts were excluded, as were reports on criteria for extubation.[21,28,29]

Data extraction and analysis

For each included study, year of publication, type of surgery, number of patients enrolled (including numbers after withdrawals), whether study design was both a double-blinded and randomized controlled trial (DB-RCT), ITM dose, and definition (if any) of "respiratory depression" were tabulated by the primary author (Table A, available as “additional material” at www.cja-jca.org). The definitions of RD were categorized as undefined (UND), a definition with RR alone (RRA), and a definition with other than RR alone (ORRA) [Table I]. Study data were entered into a Microsoft Excel spreadsheet.

Data analysis was performed using EpiInfo 2000 (version 1.1, Center for Disease Control, Atlanta, GA, USA). We attempted to identify associated factors with having an explicit definition of RD. We postulated that DB-RCTs, larger, or more recent studies would be more likely to define RD, and perhaps be more rigorous in that definition. Publication period and sample size were not normally distributed; therefore each variable was made into a binary variable. Selection of cut-off points was based primarily on maintaining approximately equitable distribution across categories. Publication period was dichotomized into approximate ten-year intervals (1980-1990 or 1991-2001) while study size was divided

TABLE I Definitions of respiratory depression

Definition	*Studies (n)*	*% of total*	*Comments*
Undefined (UND)	44	46	
RR Alone (RRA)	24	25	
Other than RRA (ORRA)			
RR and/or O_2 saturation*	6	6	
RR with O_2 saturation* and Cyanosis	2	2	
RR and/or ABGs	6	6	
ABGs alone	3	3	
Naloxone treatment	3	3	All surveys
RR with LOS	2	2	
CO_2 stimulation alone	2	2	
RR with CO_2 stimulation	1	1	
Multiple factors	2	2	
Statistical	1	1	ANOVA of RR and $PaCO_2$
Total	96	100	

* O_2 saturation includes SpO_2 and SaO_2. RR = respiratory rate; ABG = arterial blood gas; LOS = level of sedation.

TABLE II Presence of definitions according to different study variables

Study variable	*n*	*RD Defined*	*%*	*Risk ratio (95% CI)*	χ^2	*P-value*
DB-RCT						
No*	38	18	47	1.0		
Yes	58	34	59	1.2 (0.8-1.8)	1.2	0.28
Size						
< 50*	48	22	46	1.0		
≥ 50	48	30	63	1.4 (0.9-2.0)	2.7	0.10
Publication year						
1980-1990	33	19	58	1.0		
1991-2001	63	33	52	0.9 (0.6-1.3)	0.2	0.63

RD = respiratory depression; DB-RCT = double-blinded, randomized controlled trial; * Referent category.

TABLE III Definitions of respiratory depression in double-blinded, randomized controlled trials

Definition	*n*	*DB-RCT*	*%*	*Risk ratio (95% CI)*	χ^2	*P-value*
UND*	44	24	55	1.0		
RRA	24	16	67	1.2 (0.8-1.8)	0.9	0.33
ORRA	28	18	64	1.2 (0.8-1.7)	0.66	0.42

UND = respiratory depression undefined; RRA = respiratory rate alone as definition; ORRA = other than respiratory rate alone as definition; DB-RCT = double-blinded, randomized controlled trial; *Referent category.

TABLE IV Definitions of respiratory depression according to study size

Definition	*n*	*Study size ≥*	*%*	*Risk ratio (95% CI)*	χ^2	*P-value*
UND*	44	18	41	1.0		
RRA	24	13	54	1.3 (0.8-2.2)	1.08	0.30
ORRA	28	17	61	1.5 (0.9-2.4)	2.65	0.10

UND = no definition of respiratory depression; RRA = respiratory rate alone as definition; ORRA = other definition than respiratory rate alone; *Referent category.

TABLE V DEFINITIONS OF RESPIRATORY DEPRESSION ACCORDING TO PUBLICATION PERIOD

Definition	*n*	*Year > 1990*	*%*	*Risk ratio (95% CI)*	χ^2	*P-value*
UND*	44	30	68	1.0		
RRA	24	17	71	1.0 (0.8-1.4)	0.05	0.82
ORRA	28	16	57	0.8 (0.6-1.2)	0.89	0.34

UND = no definition of respiratory depression; RRA = respiratory rate alone as definition; ORRA = other definition than respiratory rate alone.

into studies with less than 50 or greater than 49 patients. Making the assumption that DB-RCTs are higher order studies and therefore more rigorous in design, study design was also dichotomized by whether or not studies were DB-RCTs. The association between publication period, study size and study design with the presence or absence of any definition of RD was assessed (Table II). The association between these same factors with a specific definition of RD (UND, RRA or ORRA) was also assessed (Tables III–V). Chi square and *P*-values were calculated to assess the probability of obtaining a specific outcome, while risk ratios and 95% confidence intervals were calculated to obtain an estimate of the magnitude and precision of the frequency of the outcome. An alpha of 0.05 and a power of 80% were used to assess for statistical significance.

Results

Systematic search

The original Medline search and hand-searching identified 209 studies. These were included if ITM use was appropriate (bolus dose, for postoperative analgesia) and the term "respiratory depression" was used. Some studies from the Medline search did not use "RD" in the text[30–34] and were thus excluded. Eventually, 96 studies were included for analysis[7,8,10–14,17,18,20–29,35–111] (Table A available online).

The search found that the earliest year of publication amongst these 96 studies was 1981.[12,13,44] This was not surprising, as the earliest published report of ITM was made in 1979.[1] Thirty-three studies (34%) were published between 1980 and 1990, while 63 (66%) were published between 1991 and 2001. Forty-eight of 96 studies (50%) involved at least 50 subjects. Fifty-eight of 96 (60%) were DB-RCT studies. There were five large-scale surveys[7,17,18,42,74] which were not considered part of this group. No case-controlled studies were found.

Data analysis

From the 96 studies of ITM for postoperative analgesia, 44 (46%) did not define "respiratory depression" (UND) despite using this term (Table I). Twenty-three of the 44 undefined studies made objective measurements, such as arterial blood gases (ABGs), but were considered UND, as specific levels were not provided.[12,13,28,46,52,58,60,63,65,68,72,77,82,83,86,90,91,95,96,99,101,105,107] A further 24 studies (25%) defined RD with RRA. Less than one-third of the studies, 28 (29%), defined RD with ORRA. The majority of this latter group defined RD with RR in conjunction with other variables, such as SpO_2 and ABGs. Six studies defined RD with both RR and ABGs,[8,14,20,74,103,109] while three used ABGs alone.[24,56,78] RR was the most common variable used to define RD.

Oxygen saturation in conjunction with RR defined RD in six studies.[25,51,64,75,88,102] Most of these studies used pulse oximetry, though Lauretti *et al.* ambiguously measured "oxygen saturations".[88] SpO_2 values ranging from "$\leq$ 85%"[25] to "$\leq$ 94%"[51] were used in the definitions. Two other studies included presence of cyanosis, RR and either oxyhemoglobin saturation from SpO_2[37] or ABG analysis[38] in their definitions.

Three large surveys defined RD by the use of naloxone treatment.[7,17,18] Rawal *et al.*[17] defined RD for their extradural group differently from their ITM group and conceded to having an "inexact" definition of RD in another survey.[18] More specific definitions were not stated, even though the surveys asked respondents for specific criteria to define ventilatory depression.[17]

There also exist less common definitions of RD. These include statistical analyses of respiratory variables,[10] RR with LOS,[26,59] and specific radiographic and/or laboratory abnormalities.[61] Johnson *et al.* defined RD with multiple criteria, including RR, $PaCO_2$, drowsiness, naloxone treatment and respiratory failure.[81] Ventilatory responses to hypercarbia alone[11,27] or along with RR[36] were used as research methods to define RD.

Many studies that did not define RD (UND) still assessed respiratory variables. For instance, Bernard *et al.*[46] compared occurrences of "RR < 10" and "SpO_2 < 90%", but defined RD by hypercapnia and requirement for naloxone. Hypercapnic $PaCO_2$ levels were undefined, although naloxone was given if $PaCO_2$ > 50 mmHg. Undefined studies also assessed RR,[52,60] level of sedation,[58] SpO_2,[65] ABGs,[107] end-tidal PCO_2,[13] presence of cyanosis,[83] apnea[12] and/or hypopnea.[54] Similarly, studies that defined RD may have additionally monitored SpO_2,[67,104] RR[24] and pulmonary function test (PFT) values[20] without using it in their definition. The reader should not infer that these measures define RD.

The frequency of RD being defined was similar between DB-RCT studies and non-DB-RCT studies (Table II); (risk ratio 1.2, 95% confidence intervals [CI] 0.8–1.8). The frequency of having any definition of RD included in the study was not significantly associated with study size (risk ratio 1.4, 95% CI 0.9–2.0). Finally, publication period (1980 – 1990 or 1991 – 2001) was also not associated with the inclusion of any definition of RD (risk ratio 0.9, 95% CI 0.6–1.3). When definitions of RD were divided into three categories (UND, RRA and ORRA) and the risk ratios calculated for DB-RCT design, study size and publication period (Tables III–V), the results remained statistically insignificant. Thus, rigorousness of RD definitions was not associated with study design, study size or publication period; however, small sample sizes also contributed to non-significant findings.

Discussion

This literature review found that almost half of studies which suggested postoperative ITM caused "respiratory depression" did not define this term. This is a worrisome observation. Surprisingly, increased prevalence of RD being defined was not associated with more recent publication periods. This latter result is of particular interest, given the advent of initiatives like the CONSORT Statement.[112]

While it is recognized that RD is a serious complication associated with ITM, the true incidence of RD remains unclear for several reasons. One reason is that

RD is a rare event, influenced by a large number of variables, which therefore requires a large number of patients to define this incidence.[102] Rare events are traditionally studied with case-control studies. However, no case-control studies were identified in the literature. Also, opioid-induced RD is confounded by hypoventilation and hypoxemia from midazolam sedation, general anesthesia and surgery itself.[4] Some studies used *iv* patient-controlled analgesia after ITM,[36,37] which may also confound ITM-induced RD. Importantly, "respiratory depression" is not a term with a clear or standard definition. Therefore, studies quoting events of RD may actually be observing different phenomena. An attempt to standardize this definition would reduce inter-observer variability and promote understanding the true incidence of the respiratory side effects with ITM.

A quarter of the studies in our review defined RD with only RR assessment. Many defined RD with a RR less than 10.[40] This method is simple, non-invasive, and the patient is not inconvenienced.[104] While defining RD with bradypnea is superior to no definition whatsoever, it is considered to be an inadequate index of ventilatory depression.[4,10,15,27,81,113–115] RR does not necessarily correlate with ITM dose, hypoxemia or depressed ventilatory response to CO_2-stimulation.[9,27] Patients may even be hypoxemic[4] or hypercapnic with a normal RR.[8,24,81,83,116,117] Conversely, patients with low RRs may compensate adequately to keep $PaCO_2$ levels within normal limits.[10] Since RR is not a reliable indicator of RD, studies using RR to evaluate RD may be underreporting the true incidence. RR may even be a poor indicator of impending apnea.[114] Therefore, we believe that RR should not be used alone to define RD.

RD has also been defined as a failure to respond adequately to hypercapnia or hypoxia.[118] This may be considered a "standard" definition of RD. Central RD exists when the respiratory neurons of the medulla fail to respond appropriately to these stimuli. Respiratory neurons also exist in other brainstem areas. Normally, the dominant control of ventilation is mediated through an increase in $PaCO_2$, which strongly stimulates central chemoreceptors,[119] leading to increased ventilation. RD from morphine is characterized by a dose-related, naloxone-reversible depression of resting minute ventilation (Ve) with proportional reduction of tidal volume (Vt),[120–122] decreased PaO_2 and pH, increased $PaCO_2$,[121,123] and decreased ventilatory drive stimulated by hypercapnia and hypoxia.[124,125] In volunteers, ITM caused a dose-related depression of medullary respiratory centre sensitivity to ventilatory stimulus.[9] Decreased chemosensitivity of the respiratory centres to hypercapnia is a sensitive index of RD.[113,126]

Ten studies defined RD with ABG values (either alone, with RR, or as part of multiple criteria). There are many advantages in defining RD with ABGs. It offers the best measurement of ventilatory adequacy, directly and quantitatively[127] reflecting the net results of gas exchange. ABGs are universally used in pulmonary function assessment.[128] With ITM, there is a dose and time-related increase in $PaCO_2$. and decrease in pH.[9] While there are no absolute levels of PaO_2 or $PaCO_2$ that indicate RD or failure, generally in those without preexisting lung disease, PaO_2 less than 60 mmHg (hypoxemia) or $PaCO_2$ more than 50 mmHg (hypercarbia) were used.[8,129] Disadvantages of using ABGs include its invasiveness, time delay for results, intermittent frequency, and possible lack of correlation with ventilatory response to hypercapnia and hypoxemia.[27] Since invasiveness is a concern, its use should be minimized where possible.

Clinically, hypercapnia appears to provide the most rigorous definition of "respiratory depression", as RD has been defined classically as "a failure to respond adequately, on a moment-to-moment basis, to hypercapnia or hypoxia".[118] However, the most practical and effective method for detecting hypoxemia and/or hypoventilation after ITM is unknown.[5,104] Perhaps the term "respiratory depression" should only be used for experimental situations, when there is a depressed ventilatory response to hypercapnia or hypoxemia. Then, a low RR would be better referred to as "bradypnea" and not "respiratory depression". Similarly, a low SpO_2 would be preferably termed "hypoxemia".

Conclusion

The term "respiratory depression" has no clear definition from a review of the literature involving ITM for postoperative analgesia. Approximately half of these studies did not even define the term, despite using it. This makes it difficult to ascertain the true respiratory risks of this technique. The inclusion of any definition of "respiratory depression" was not associated with DB-RCT, sample sizes of greater than 49 subjects or publication after 1990. The rigorousness of RD definitions was also not associated with these study variables.

In future research, the consistent use of terms with specific meanings, as opposed to the ambiguous catch-all term "respiratory depression", will facilitate understanding the true incidence of ITM's respiratory effects. If "respiratory depression" is used, then an explicit definition of its meaning should be clearly provided. Future research must also address what is clinically significant respiratory impairment from intrathecal opioids, and how to optimally monitor for these effects. Further delineating their risks *vs* benefits will allow for more optimal dosing determinations.

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