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Inhaled analgesia for labor pain

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Abstract: Labour pain is one of the most sever pains in the life of women. It is multifactorial and affected by both psychological, many biochemical and physiological factors. Many methods are used to manage labour pain whichare divided into pharmacological and non-pharmacological methods.
Inhaled analgesia, as part of the pharmacological methods, involves the inhalation of smaller dose of the inhaled anaesthetic agents while maintaining awareness of the mother.Drugs used for inhaled analgesia for relief of labour pain include nitrous oxide, isoflurane, sevoflurane, trichloroethylene, methoxyflurane and cyclopropane.
It is important to do this review because all women should have a relatively effective and safe analgesia during labour. Therefore, this review objective was to explore the efficacy and safety of inhaled analgesia as pain relief for women in labour planning a vaginal delivery.A total of 74 reports of studies were identified from the search strategy. A total of 26 studies reporting data on 2959 women (31 reports) were included and 27 studies (43 reports) were excluded. Outcomes included effect of inhaled analgesia on pain intensity, pain relief,satisfaction with pain relief, effect of inhaled analgesia on assisted vaginal birth, caesarean section, nausea, vomiting, drowsiness, amnesia, and Apgar score less than seven at five minutes.
This review concluded that inhaled analgesia may be beneficial for labour pain relief, with minimal to no effect on Apgar score of the newborn.There is a need for adequately powered randomised controlled trials which include relevant clinical outcomes.

Key words: *Labour pain, Inhaled analgesia, Nitrous oxide, Flurane derivatives, Pain intensity, Pain relief, amnesia, Apgar score, TENS.*

I. BACKGROUND

Labour pain is one of the most sever pains in the life of women. It is multifactorial and affected by both psychological, many biochemical and physiological factors[1, 2]. Recognition of labour pain varies. Occasionally women feel no pain in labour,while in the other hand, labour pain has been described as the most severe pain that a woman experiences in her lifetime [3], [4]. Therefore, reliving labour pain is one of the main concerns for pregnant women, healthcareattendants and the general public[5]. These methods to relief labour pain have implications on the course of labour, quality of mother and baby outcomes and the cost of obstetric care.

During labour pain originates from different sites during each stage of the labour and delivery process. In the first stage of labour (defined as the period from the onset of labour to the complete dilatation of the cervix)[6], pain occurs during contractions. It is cramp-like pain. It is originated in the uterus and cervix by distension of uterine tissues and dilation of the cervix. This pain is transmitted via spinal nerves T10-L1. Because of that, this pain can be referred to the abdominal wall, lumbosacral region, iliac crests, gluteal areas, and thighs. Usually, primiparas experience greater pain than multiparous women, typically during early labour before 5 cm dilatation[1]. The chosen positions by woman during labour may affect her feeling of pain[7, 8],[9]. It was found that women using upright or lateral position report less severe pain than women lying on their back during labour. In the other hand, Women may experience less pain during spontaneous labour than induced labour[10].Psychosocially,many factors influence women's experience of labour pain including previous delivery experiences, culture, ethnicity and education[1].

Now a day,general public has a negative belief of pain, that it is barbaric and should not be suffered by any one. A wide range of pain management methods are used by women during childbirth[5]. These are either, non-pharmacological methods and pharmacological methods. Non-pharmacological methods help women cope with pain in labour and includes hypnosis, biofeedback, subcutaneous sterile water injection, immersion in water, aromatherapy, relaxation techniques (yoga, music, audio), acupuncture, manual methods (massage, reflexology), and transcutaneous electrical nerve stimulation (TENS). On the other hand, pharmacological methods relieve the pain of labour and includes inhaled analgesia, opioids, non-opioid drugs, local anaesthetic nerve blocks, epidural and intrathecal injections of local anaesthetics or opioids, or both[11]. From the above, we recognize that pain in labour is multifactorial and with some overlap between factors. Added to that, some pain relief methods are explained and exercised in antenatal classes then it isusedbefore to the onset of labour,

for example, hypnosis and use of TENS. On the contrary, otherpain relief methods are administered only during labour,for example, inhaled analgesia.

Inhaled analgesia during labour defined as the inhalation of sub-anaesthetic concentrations of agents while the mother remains awake. Historically, inhaled analgesics was used for the first time for relief of labour pain in 1847 by James Simpson[12]. While, Stanislaw Klikovich was the first to use nitrous oxide 80% in oxygen in 1881 on women in labour[13]. However, Minnitt was the first to introduce an apparatus for the self-administration of nitrous oxide In 1934[14].

Drugs used as inhaled analgesia for pain relief in labour are nitrous oxide, isoflurane, sevoflurane, trichloroethylene, methoxyflurane and cyclopropane. Trichloroethylene and cyclopropaneare not used anymore in the developed world because the first is flammable, while the second is explosive. On the other spectrum, sevoflurane is not used because it has no analgesic activity at sub-anaesthetic concentrations. This leaves us with, nitrous oxide, enflurane, isoflurane and methoxyflurane. These medications do not decrease uterine contractions and that's why they are preferred. However, nitrous oxide use is widespread in modern obstetric wards because it is easyto administer, lack flammability, lack odour, has no effect on uterine contractions, has minimal toxicity and minimal depression of the cardio-vascular system[15, 16].Inhaled analgesics are characterized by theirlow blood/gas solubility ratio, which is due to their rapid uptake/washout rate. Therefore, at 37 Co the blood/gas solubility ratio for nitrous oxide is 0.47; for Isoflurane is 1.4; for Sevoflurane is 0.69; for Enflurane is 1.64 and for Methoxyflurane is 13.

Methoxyflurane is more potent than all the other inhaled analgesic drugs in spite of its low solubility, therefore, it is still used in some obstetrics wards. On the other hand, nitrous oxide maximal effect can be obtained in 30 to 60 seconds and wash-out in three or four exhalations[17]. However, there is argument about the use of nitrous oxide because of few safety concerns for female care givers[18-24]. Nitrous oxide characteristically inactivate methionine synthase in the cells which can affect female care givers fertility[25]. This cellular-level damage starts during a maternity-care worker's shift, but it will happen only in a poorly ventilated hospital where nitrous oxide is used without cleaning of the gas. Furthermore, the damage produced stops when the care worker leaves the hospital by the process of restitution, but, as she returns to work in the same environment before restitution is complete, the damage-producing process resumes and over time, the damage may accumulate enough to produce pathology[23]. This pathology may decrease the fertility of female care givers or increase their risk of spontaneous abortion, but this risk can be stamped out in well ventilated modern hospitals[23, 26].

Inhaled analgesia, in general if used too long or extensively may cause maternal drowsiness, nausea and vomiting. It is uncertain how inhaled analgesia relief pain, otherwise, the suggestion that these drugs induces the release of endogenous opioidsin the midbrain, which, could balance labour pain stimuli through the descending spinal cord nerves[27].

It is important to do this review because all women should have a relatively effective and safe analgesia during labour[26]. Added to that, it is important to have other options for pain relief during labour in view of the side effects of the invasive options.

II. METHODS

The objective of this review is to explore the efficacy and safety of inhaled analgesia for labour pain relief in women planning vaginal delivery. Therefore, without language restrictions, major journals and databases were searched for randomized controlled trials (RCTs) and studies with a cross-over design. Participants of these studies and trials are women in labour excluding women in high-risk groups, for example,pregnancy induced hypertension or gestational diabetes.Interventions were any inhaled analgesia during first stage of labour, with any frequency or duration of administration, any dosage, and any combinations. Outcomes used to study the effect of inhaled analgesia were pain intensity, pain relief and satisfaction with pain relief. For the safety of inhaled analgesia, we studied the outcomes of assisted vaginal birth, caesarean section, nausea, vomiting, drowsiness, amnesia and Apgar score less than seven at five minutes.

Statistical analysis was carried out using the Review Manager software[28]. For data studying the same effect,fixed effect meta-analysis was used. In the other hand, if heterogeneity (expressed in the analysis as T^2 and I^2) was more than 25%random-effects analysis was used.

III. RESULTS

A total of 74 reports for 53 studies were identified. A total of 26 studies reporting data on 2959 women (31 reports) were included, while, 27 studies (43 reports) were excluded.

Of the included studies, eighteen were parallel design[17, 29-46] and eight cross-over design[47-54]. One study had two parts [50]; the second part was a randomized cross-over study, which was only used for analysis, unfortunately, there was no data from this part. Two studies had three arms [33, 42]and all the remaining studies

had two comparison arms. We did not include the third arm of these two studies which were the control arms (no treatment). The main comparison groups included:
studies comparing one type of inhaled analgesia with another type of inhaled analgesia[29, 30, 32, 33, 37, 38, 42, 43, 46-48, 51-54];studies comparing the same types of inhaled analgesia of different strengths[34, 39];studies comparing the same types of inhaled analgesia using different delivery systems[31, 35];studies comparing inhaled analgesia with placebo control/no treatment[17, 33, 36, 40-42, 44, 45, 55];and one study comparing inhaled analgesia with TENS [50].

Of the excluded studies, eight were not randomised controlled trials[56-63] and six studies used quasi methods of randomization [64-69]. In four studies, they were investigating the effect of general anaesthesia in women undergoing caesarean section and not during childbirth[54, 70-72] and in four studies the comparison drugs are no longer used in practice (trichloroethylene; cyclopropane)[61, 66, 73, 74]. In five studies the comparison interventions were opioids, epidural or other multidrug interventions and therefore did not meet the inclusion criteria[75-79].

We included data from 23 trials (2599 women) using different modalities of inhaled analgesia for pain management in labour for our meta-analyses. In three studies[41, 44, 49], data could not be included in the meta-analyses. In the Carstoniu 1994 study[49], data were not reported in a form that could be included in the meta-analyses (only in figures). In Shao 2000 and Wang 1994[41, 44], the data are limited in the translation of the papers, which were not published in English. We included only the data of the first period before the first cross over for the Wee 1993[53] cross-over trial, because the data from the second and third periods were incomplete. Wee 1993[53]was analysed as if the trial was a parallel group study design. We used the data from the whole of each intervention period for the following four cross-over studies Arora 1992, McGuinness 1984, McLeod 1985 and Yeo 2007[47, 51, 52, 54]and analysed the data as if it were from a parallel study. We did not combine results from parallel and cross-over studies in the analyses, but analysed these separately.

III.I) Inhaled analgesia nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives)

I.1) Pain intensity

Pain intensity was measured using a visual analogue scale(VAS) from 0 to 100 mm, where 0 corresponds to no pain at all and 100 correspond to the worst pain. Three studies with 123 measurements of 70 women reported on this outcome.

The Flurane derivatives group reported a lower intensity of pain compared with the nitrous oxide group (average mean difference (MD) 14.39, 95% confidence interval (CI) 4.41 to 24.37), Figure 1.

I.2) Pain relief

The Flurane derivatives group reported better pain relief compared with the nitrous oxide group (MD -16.32, 95% CI -26.85 to -5.79).

I.3) Satisfaction with pain relief

Satisfaction with pain relief assesses to what extent women are satisfied with the form of pain relief. It was reported in two studies with 98 women. There was no difference in satisfaction with pain relief for women receiving methoxyflurane (continuous (mean 0.22%) or intermittent (0.35%)) compared with women receiving nitrous oxide (continuous (41.2%) or intermittent (50%)) (risk ratio (RR) 0.97, 95% CI 0.80 to 1.18), Figure 2.

I.4) Assisted vaginal birth (vacuum extraction or forceps)

Numbers of assisted vaginal births are given in five studies[29, 30, 32, 37, 42] with 371 women. There were no differences between women receiving nitrous oxide and those receiving a Flurane derivative (RR 0.71, 95% CI 0.44 to 1.15), Figure 3.

I.5) Caesarean section

Caesarean section was reported in one trial[32] with 98 women. There were no caesarean sections in either group.

I.6) Amnesia

Amnesia in womenwas reported in three studies with 245 women. There was less amnesia in nitrous oxide group compared to desflurane group (RR 0.09, 95% CI 0.02 to 0.48).

I.7) Drowsiness

Drowsiness was scored with VAS from 0 to 100 mm, was reported in one study with 18 women. There was no difference in drowsiness between the nitrous oxide group and the Isoflurane group (MD -11.64, 95% CI -16.04 to 39.32), Figure 4.

I.8) Nausea

Nauseawas reported in two trials with 98 women. The nitrous oxide group reported more nausea compared with the Flurane derivatives group (RR 6.60, 95% CI 1.85 to 23.52), Figure 5.

I.9) Vomiting

Vomiting was reported in three trials with 203 women. There was no difference in vomiting between nitrous oxide group compared with the Flurane derivatives group (RR 2.02, 95% CI 0.75 to 5.46), Figure 6.

I.10) Apgar score less than seven at five minutes

This was reported in five trials [29, 30, 32, 42, 46]with 373 women with single births. Two babies were reported with an Apgar score of less than seven at five minutes postpartum in the Flurane derivatives group in one study, and none in the nitrous oxide group (RR 0.22, 95% CI 0.01 to 4.47), Figure 7. There were no low Apgar scores in the other trials.

No trials reported on any cost outcome.

III.II) Inhaled analgesia (same type) of one strength versus a different strength

II.1) Satisfaction with pain relief

It was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70%. There was no difference in satisfaction with pain relief (RR 1.05, 95% CI 0.94 to 1.17), Figure 8.

II.2) Caesarean section

It was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70%. There was no difference in caesarean section rate between groups (RR 0.31, 95% CI 0.06 to 1.53), Figure 9.

II.3) Assisted vaginal birth

This was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70%. There was no difference in assisted vaginal birth rate between groups (RR 0.83, 95% CI 0.61 to 1.14), Figure 10.

II.4) Vomiting

Vomiting was reported in one study with 501 women comparing nitrous oxide 50% with nitrous oxide 70%. There was no difference between groups (RR 1.29, 95% CI 0.86 to 1.94), Figure 11.

No trials reported on any other outcomes.

III.III) Inhaled analgesia using one type of delivery system versus a different system

III.1) Satisfaction with pain relief

This was scored on one study with 42 women. The study compared nitrous oxide 50% with nasal supplement of nitrous oxide 50% versus nitrous oxide 50% and no supplement. There was no difference in satisfaction with the pain relief between groups (RR 1.18, 95% CI 0.94 to 1.48), Figure 12.

III.2) Vomiting

Vomitingwas reported in one study with 49 women. The study compared nitrous oxide 50% with continuous nasal supplementation of nitrous oxide 50% versus nitrous oxide 50% with no inhalation. There was no difference in vomiting between groups (RR 1.76, 95% CI 0.77 to 4.00), Figure 13.

III.3) Apgar score less than seven at five minutes

It was reported in one study with 26 women. There was no difference in Apgar scores between groups (MD 0.00, 95% CI -0.37 to 0.37), Figure 14.

No trials reported on any other outcomes.

III.IV) Inhaled analgesia versus placebo control or no treatment

IV.1) Pain intensity

Pain intensity during the first stage of labour reported as clear, severe to intense or extreme in two studies with 310 women. The inhaled analgesia group of nitrous oxide 30% to 50% reported less pain compared with the control (O2 100%) or no treatment group (average RR 0.06, 95% CI 0.01 to 0.34), Figure 15.

IV.2) Assisted vaginal birth

This was reported in one study with 200 women. The study compared nitrous oxide 50% versus no treatment. There was no difference in assisted vaginal births between groups (RR 1.50, 95% CI 0.44 to 5.15), Figure 16.

IV.3) Caesarean section

Caesarean section was reported in three studies with 465 women. The studies compared nitrous oxide 30% to 50% versus no analgesia or oxygen 100%. There was no difference between groups (RR 1.20, 95% CI 0.75 to 1.91), Figure 17.

IV.4) Vomiting

It was reported in two studies with 619 women. The studies compared nitrous oxide 30% to 50% versus oxygen 50% to 100%. The nitrous oxide group reported more vomiting compared with the oxygen group (RR 9.05, 95% CI 1.18 to 69.32), Figure 18.

IV.5) Apgar score less than seven at five minutes

This was reported in one study with 200 women. The study compared nitrous oxide 50% versus no analgesic use, with no difference between groups (RR 9.00, 95% CI 0.49 to 165.00), Figure 19.

No trials reported on any other outcomes.

III.V) Inhaled analgesia versus TENS

V.1) Satisfaction with pain relief

Satisfaction with pain relief was reported in one study with 20 women. The study compared nitrous oxide 50% versus TENS. There was no difference between groups (RR 0.56, 95% CI 0.29 to 1.07), Figure 20.

No trials reported on any other outcomes.

IV. DISCUSSION

Results of meta-analysis authenticate that Flurane derivatives are better than nitrous oxide when used as inhaled analgesia during the first stage of labour for the relief of labour pain, with less reports of nausea. Anyhow, caution should be suggested since this result was extracted from the analysis of onlyfive studies[47, 51-54]. We reported on drowsiness as an outcome to examine the safety of the intervention, however, drowsiness is often seen as a valuable side effect.

Meta-analysis also, showed that when comparing self-administered (intermittent) nitrous oxide 50% and no treatment, women reported less pain intensity. On the other hand, comparing intermittent nitrous oxide 30% to 50% to oxygen 50% recorded more vomiting, nausea, dizziness and drowsiness.Again, caution should be advised when examining these results since the data was obtained from meta-analysis of three studies only.

Regarding comparing strength versus a different strength, different delivery systems comparing inhaled analgesia with TENS there were no significant differences found for any of the outcomes.

The conclusions should be considered with caution since, every meta-analysis was performed in the context of small sample sizes (range 20 to 380). Of the included studies only fivehad a sample size of more than 200. Blinding was seldomely achieved in many studies, this was on the ground that many inhaled analgesics had a smell. On the other hand, there was a large limitation to the completeness and applicability of the included studies and no study at a low risk of bias.Moreover, many studies oversight clinical safety outcomes. As well as, the presence of small numbers of trials within comparisons and lack of high-quality trials indicates insufficient evidence of a treatment effect from inhaled analgesia. On these grounds, caution and limitation of the results interpretation should be exercised.

Flurane derivatives use is not widespread in obstetrics wards compared to nitrous oxide. However, both Flurane derivatives and nitrous oxide are relatively inexpensive. Added to that, nitrous oxide had no sharp smell. But the main difference is in the ease of administration, since nitrous oxide can be administered by women themselves with the right equipment and on the other end of the spectrum, Flurane derivatives must be controlled by well-trained anesthetist. This is to ensure the right concentration of the agent and this way preventing unconsciousness or any other problems.

V. CONCLUSIONS

Inhaled analgesia may be beneficial for those women in labour who want to have pharmacological pain relief, without invasive methods, and with minimal to no effect on Apgar score of the newborn.

There is a need for adequately powered randomised controlled trials which include relevant clinical outcomes.

VI. CONFLICT OF INTEREST

None known.

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Figures

Figure 1: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for the outcome of pain intensity

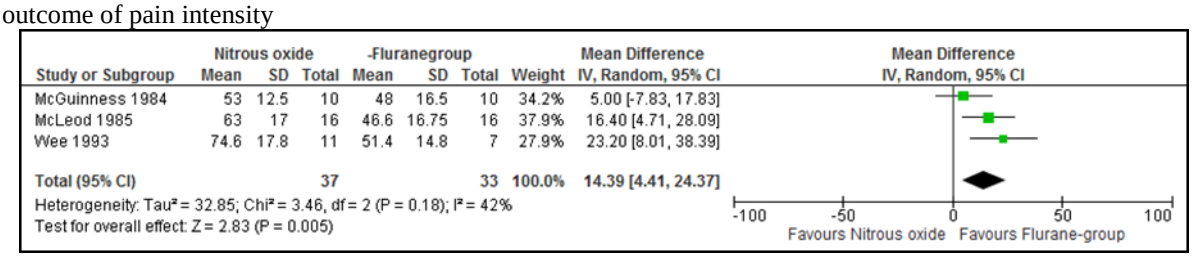

Figure 2: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for satisfaction with pain relief

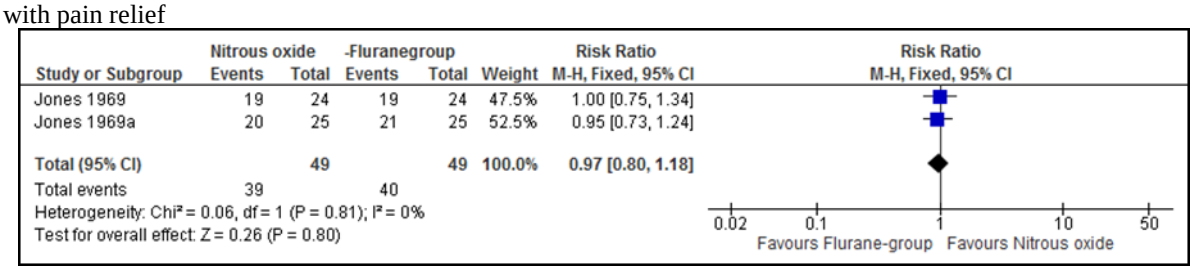

Figure 3: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for assisted vaginal birth

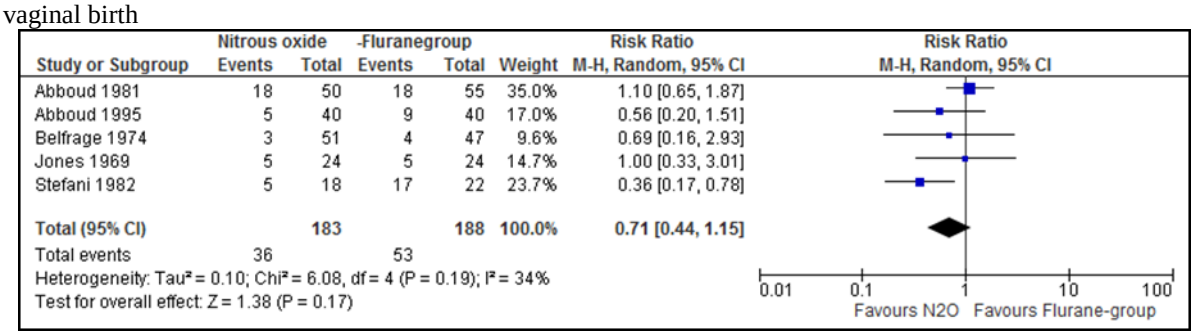

Figure 4: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for drowsiness

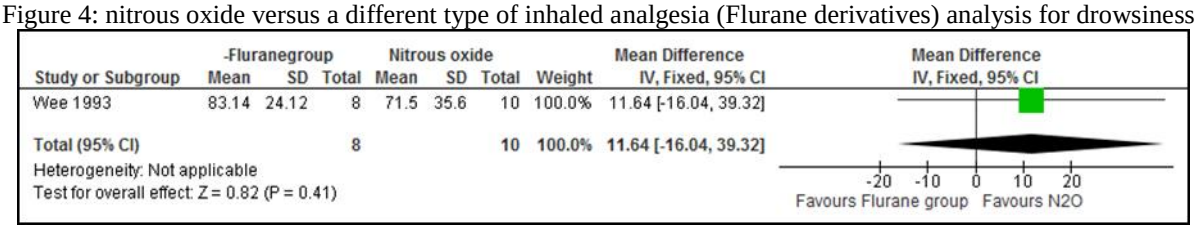

Figure 5: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for nausea

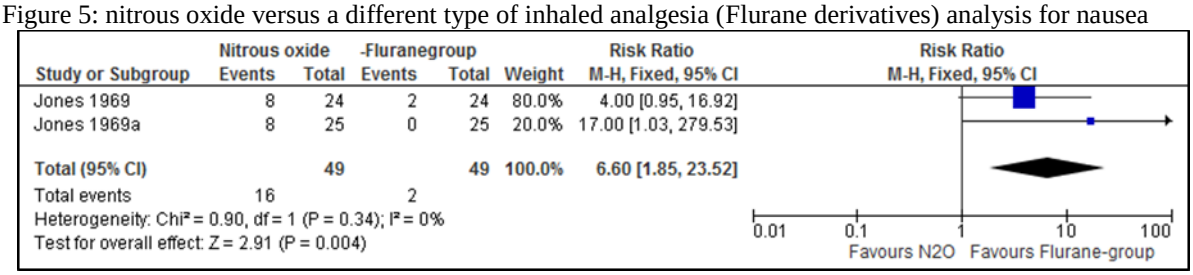

Figure 6: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for vomiting

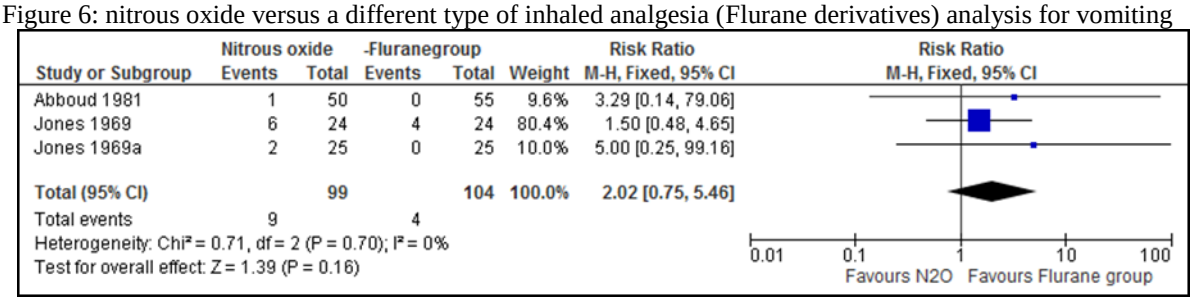

Figure 7: nitrous oxide versus a different type of inhaled analgesia (Flurane derivatives) analysis for Apgar score less than seven at five minutes

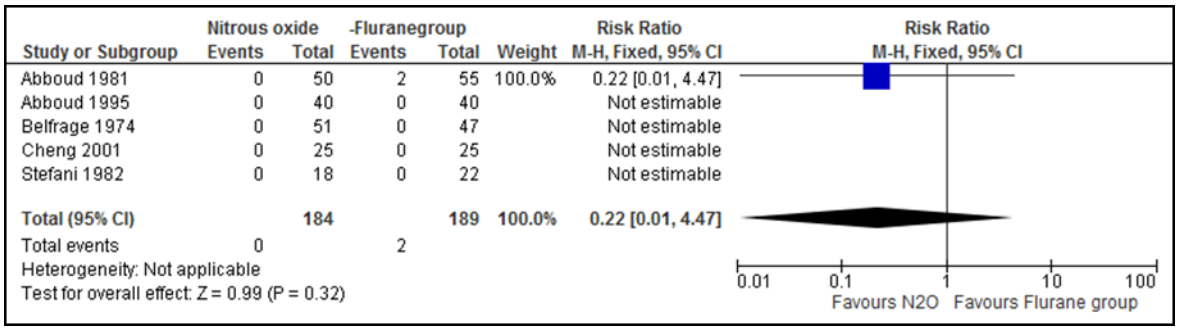

Figure 8: Inhaled analgesia (same type) of one strength versus a different strength analysis for satisfaction with pain relief

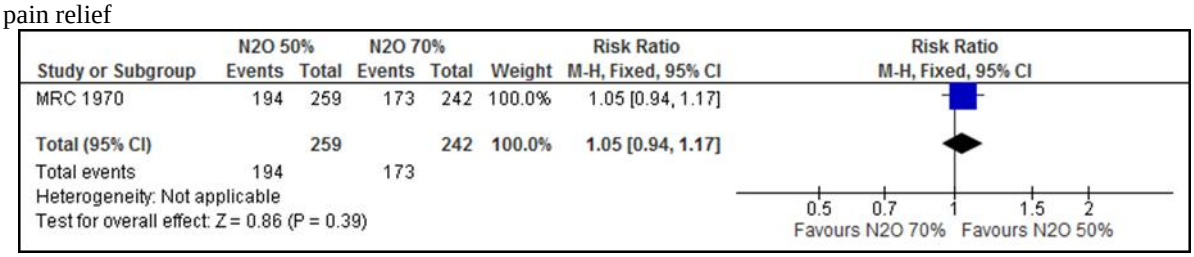

Figure 9: Inhaled analgesia (same type) of one strength versus a different strength analysis for caesarean section

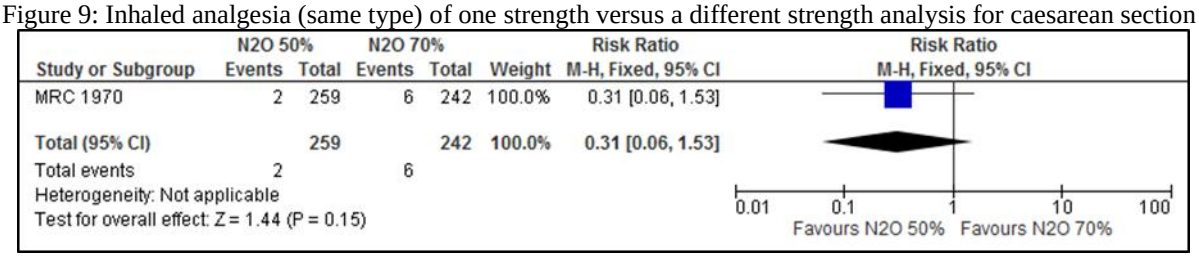

Figure 10: Inhaled analgesia (same type) of one strength versus a different strength analysis for assisted vaginal birth

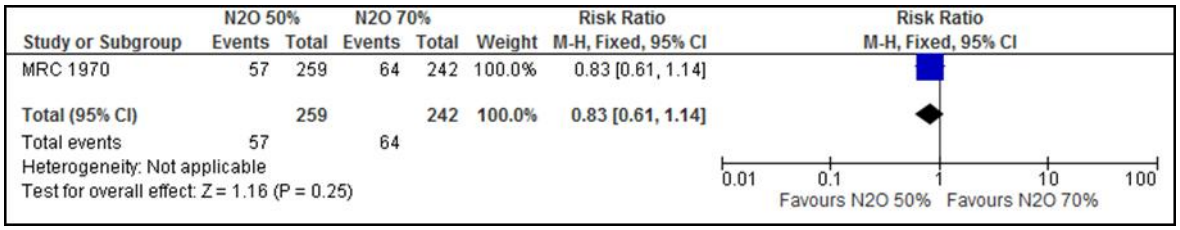

Figure 11: Inhaled analgesia (same type) of one strength versus a different strength analysis for vomiting

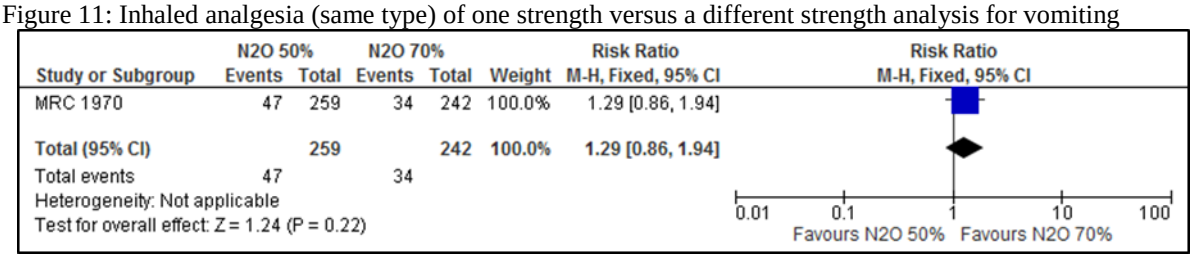

Figure 12: Inhaled analgesia using one type of delivery system versus a different system analysis for satisfaction with pain relief

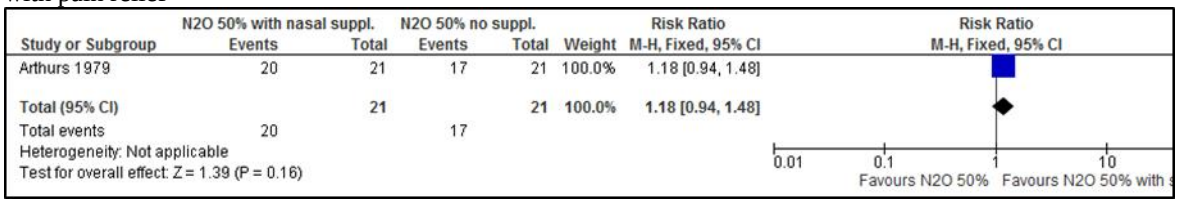

Figure 13: Inhaled analgesia using one type of delivery system versus a different system analysis for vomiting

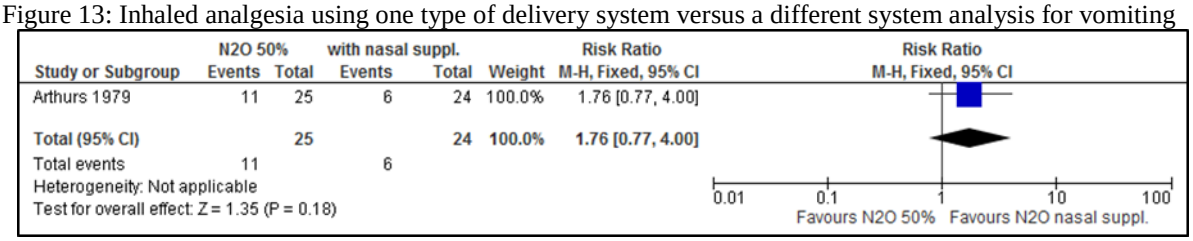

Figure 14: Inhaled analgesia using one type of delivery system versus a different system analysis for Apgar score less than seven at five minutes

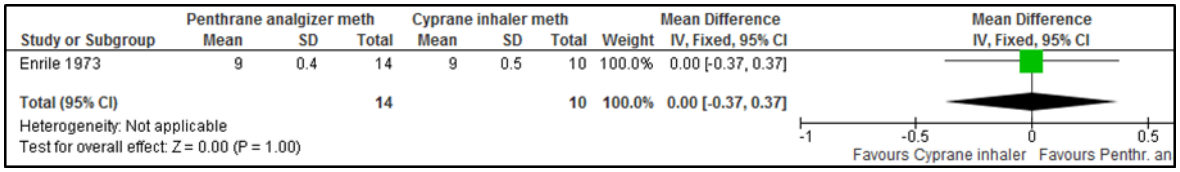

Figure 15: Inhaled analgesia versus placebo control or no treatment analysis for pain intensity

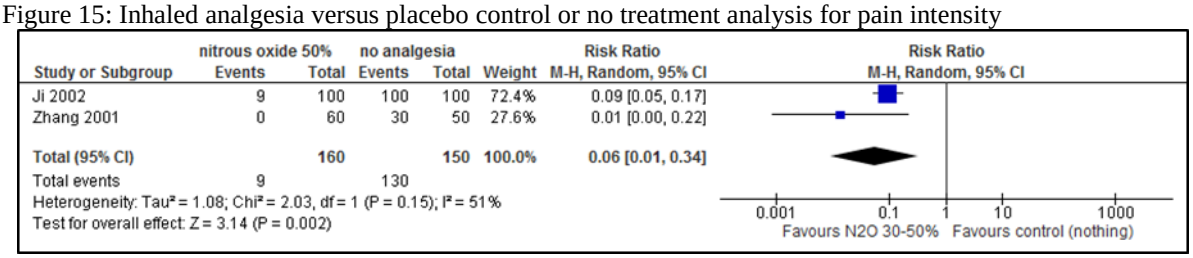

Figure 16: Inhaled analgesia versus placebo control or no treatment analysis for assisted vaginal birth

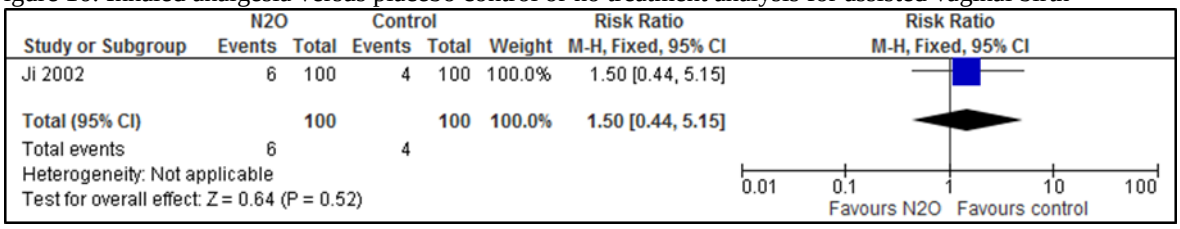

Figure 17: Inhaled analgesia versus placebo control or no treatment analysis for caesarean section

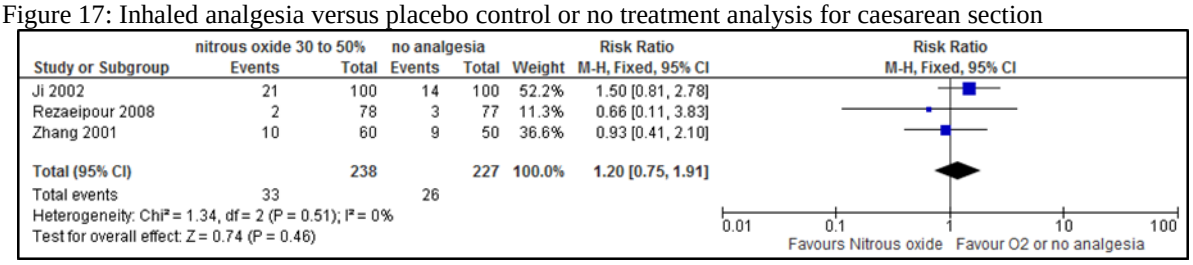

Figure 18: Inhaled analgesia versus placebo control or no treatment analysis for vomiting

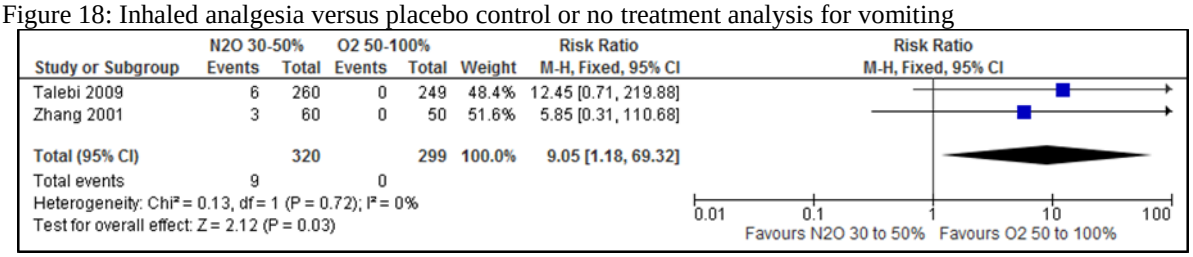

Figure 19: Inhaled analgesia versus placebo control or no treatment analysis for Apgar score less than seven at five minutes

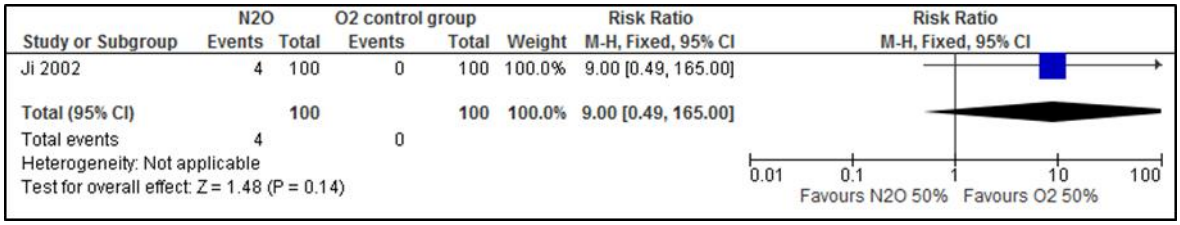

Figure 20: Inhaled analgesia versus TENS analysis for satisfaction with pain relief