Role of Corticosteroids in the Management of Acute Traumatic Brain Injury: Literature Review and Critical Appraisal of Evidence

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ABSTRACT Background: Traumatic brain injury is a prominent and leading cause of premature mortality and disability. Corticosteroids were widely used in the clinical management of traumatic brain injury, but their benefit has been challenged in so many studies and their efficacy, but their use in TBI remains unclear. This review aims to evaluate the effectiveness and efficacy of corticosteroids in reducing mortality or morbidity in people with acute traumatic brain injury. **Methods:** A systematic literature searches as enabled a thorough and robust process of rigorous critical appraisal to make an informed, balanced and evidence-based judgement on the use of corticosteroids in the management of acute traumatic brain injury to quantify the effectiveness of corticosteroids in reducing mortality and morbidity in reducing traumatic brain injury. **Results:** A systematic literature search is relevant to corticosteroid use in acute traumatic brain injury. The search strategy involving database including Embase, MEDLINE, Cochrane Database of Systematic Reviews Seven studies have been critically appraised to determine the effectiveness and efficacy of corticosteroid use in acute traumatic brain injury. **Conclusion:** It can be safely concluded that there is no significant benefit or efficacy of the use of corticosteroid in the management of acute traumatic brain injury. There is no reduction in mortality with the use of corticosteroid. However, progesterone use caused no discernible harm and showed possible sign of benefit but in a very small and single institution study. Overall the efficacy of amino-steroids in patients with moderate and severe head injury could not be demonstrated.

KEYWORDS Traumatic brain injury; head injury; corticosteroid, critical appraisal

Background

Traumatic brain injury (TBI) is defined as an alteration in the function of the brain or evidence of brain abnormalities caused by an external agent such as the head being struck by an object or the head striking an object, blast and explosion [1]. Every year, millions of peoples are treated for head injury worldwide, traumatic brain injury is a significant cause of death, prolonged and lifelong disability in young patients such as cognitive impairment in thinking, memory and reasoning especially in severe traumatic brain injury [2]

Cerebral oedema constitutes one of the fatal problems in Neurosurgery especially in a tumour and traumatic brain injury or following extensive neurosurgical resection. Hence since the introduction of corticosteroids by Galicich and French [3] with documented evidence of the beneficial effect of steroids in the management of cerebral oedema due to a primary and metastatic tumour, there have been numerous publications on the effectiveness of corticosteroids in Neurosurgery. However, the efficacy of corticosteroid therapy in the treatment of severe

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traumatic brain injury remains controversial.

The use of corticosteroids to treat acute traumatic brain injury has been in existence for more than 30 years after early reports of beneficial effects in a patient with cerebral oedema from a tumour or surgery [3]. The time interval between head injury and irreversible brain swelling and brain death allow for therapies that can reduce and limit brain swelling thus having the propensity to improve overall outcome positively, but biases in studies or previous review can mask this positive outcome. On the other hand, corticosteroids may not affect the outcome; previous UK study found that corticosteroid was used in less than half of the intensive care unit surveyed in the management of traumatic brain injury [4]. Corticosteroids decrease the production and release of pro-inflammatory cytokines [5] and may inhibit lipid peroxidation caused by oxygen radical [6].

Numerous corticosteroids have been used in traumatic brain injury management including dexamethasone, methylprednisolone, betamethasone, cortisone, prednisolone and triamcinolone [7]. It is thought that benefit may be due to a reduction in raised intracranial pressure (ICP) and also has neuroprotective activity.

The guideline for the management of severe head injury says that use of glucocorticoid is not recommended for improving morbidity outcome or reducing intracranial pressure. (America Association of Neurological Surgeon, Brain Trauma Foundation 1995 The EBIC (European Brain Injury Consortium) state that there was no established indication for the use of steroids in acute head injury management [8].

The aim of this review is to analysis and synthesis of available best evidence of safety and capable of corticosteroids in acute traumatic brain injury in comparison to using of placebos.

Methodology

A formal search of the relevant to corticosteroid use in acute traumatic brain injury. The search strategy involving database including Embase, Medline, Cochrane Database of Systematic Reviews. With the possible risk of introducing language bias, the search was limited to the English language as a result of an inability to translate from other languages hence publication for discussion will be limited to this search. Publications included were from inclusion date of 1980 to 2017 to allow room for more publication. Search was streamlined randomised controlled trials of corticosteroid use in acute traumatic brain injury. Paediatric patients were excluded as this population could not be generalised. Also non-traumatic and penetrating head injury excluded.

Results

A systematic and rigorous literature search of database yielded 140 articles, after removal of duplicate and non-relevant studies 19 full test articles were retrieved. Furthermore, seven studies were retrieved for qualitative analysis [Figure 1]

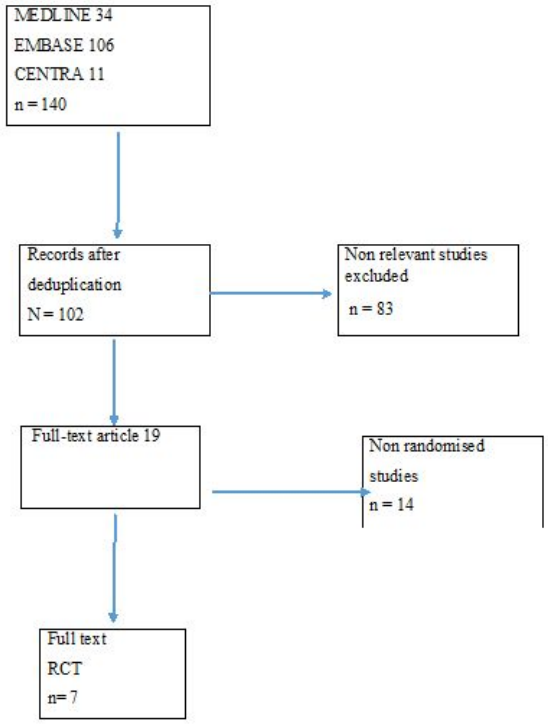

Figure 1: Search flow

Discussion

Summary of Evidence

Wright et al. [9] conducted the ProTECT trial which is a randomised clinical trial of progesterone for acute traumatic brain injury. This is based on the laboratory evidence that progesterone has potent neuroprotective effects. Hence in the light of the preclinical evidence, the goal of this study is to evaluate the efficacy of intravenous progesterone in the treatment acute traumatic brain injury. There have been animal studies in traumatic brain injury demonstrating neuro-protection for progesterone but no human clinical trial until now. Progesterone is said to be present in the brains of men and women in small but roughly equal concentrations. This study was a phase II, randomised, a placebo-controlled clinical trial with the primary objective of assessing the safety of administering progesterone to patients with moderate to severe acute traumatic brain injury. Adverse and serious adverse event rates were similar in both groups. No serious adverse events were attributed to progesterone, patients randomised to progesterone had a lower rate of 30-day mortality than control. In essence, moderate traumatic brain injury patients who received progesterone were more likely to have a moderate to a good outcome than those randomised to placebo.

This is a small study though progesterone caused no discernible harm and showed possible signs of benefit in adult patients with traumatic brain injury. Also, this study is a single institution based study, a more extensive trial involving multiple clinical centres with 1:1 randomisation and rapid commencement of treatment are needed to justify the safety of progesterone in traumatic brain injury further. This study is level 1- in the hierarchy of evidence.

Xiao et al. [10] conducted a randomised controlled trial on improved outcome from the administration of progesterone for patients with acute severe traumatic brain injury. This clinical study aimed to assess the long-term efficacy of progesterone on the improvement in neurologic outcome of patients with acute severe traumatic brain injury. This aim was strictly adhered judging from the conclusion of this study.

This study is a prospective, randomised, placebo-controlled, double-blind study with subjects enrolled to either receive pro-

Table 1 Study characteristics

Study	Methods	Title
Braakman 1983	RCT	Megadose steroids in severe head injury
CRASH 2005	RCT	Effect of intravenous corticosteroids on death within 14 days in 1008 adult
Dearden 1986	RCT	Effect of high dose dexamethasone on outcome from severe head injury
Grumme 1995	RCT	Treatment of patients with a severe head injury with triamcinolone
Wright 2006	RCT	A randomised clinical trial of progesterone for acute traumatic brain injury
Xiao 2008	RCT	Improved outcomes of progesterone for patients with acute severe traumatic brain injury: a randomised controlled trial
Marshall 1998	RCT	A multicentre trial on the efficacy of using tirilazad mesylate in cases of head injury

gesterone or matching placebo within 8 hours of documented injury. Randomisation process was of the random variables in a double-blind manner, progesterone and placebos were supplied via identical looking solution in identical glass via with or without progesterone. After the screening of 230 patients, 159 patients were randomised to both progesterone (82) and placebo (77). After 3 months and 6 months of treatment, Glasgow Outcome Scale analysis exhibited more favourable outcomes among the patients who were given progesterone in comparison with placebo. Past reports have shown evidence of efficacy in traumatic brain injury in animal models.

From this study, it can be inferred that patients with acute severe traumatic brain injury do well with progesterone regarding neurologic outcome up to 6 months. However, this study is a single-centre trial and local perioperative standard of care hence this study cannot be sufficiently generalised, the study was not powered adequately to assess progesterone's effect on the neurologic outcome. Further studies are needed to determine the mechanism of action responsible for the observed neurologic effects. This is good and well-conducted randomised controlled studies, this is a level 1 + evidence.

CRASH studies [11] conducted by crash collaborators is a multicentre international collaboration aimed to confirm or refute the fact that corticosteroids reduce the risk of death by 1-2% as suggested in systematic review findings in 1997. This is a randomised, placebo-controlled trial included adults older than 16 years with a Glasgow Coma Scale (GCS) score of 14 or less within eight hours of injury were randomly allocated 48 hours' infusion of corticosteroids (methylprednisolone). More than 10,000 patients with mean age of 37 years were recruited from 239 hospitals in 49 countries divided into 5,007 patients for the treatment group in comparison to the 5,001 in the placebo group. This is currently the largest trial on corticosteroid use in traumatic brain injury carried out in various countries hence this enhances the generalizability positively. However, no centre from North America was included in this study though challenging to imagine; possibly the results would have differed were the study from North America included.

The methodology of this study typify a well carried out research, the sheer size of this trial is very enormous especially considering the logistics of conducting a blinded placebo trial. The researcher a 96.7% six months follow up which is a good outcome for long-term follow up in comparison with most neurosurgical studies. The primary outcomes were death at two within two weeks of injury and death or disability at six months. Injury severity assessed by Glasgow Coma Scale at randomisation and pre-specified group analysis. The analysis was by intention to treat. Inclusion criteria were a traumatic head injury in adults more than 16, with GCS of 14 or less with eight hours of head injury. Eligible patients were randomised to receive intravenous methylprednisolone (Depro-Medro) therapy or placebo. They were matched for age, sex, injury time, GCS score and pupil reactivity. The treatment group received a loading dose of methylprednisolone 2g over one hour followed by 0.4g per hour for 48 hours. Approximately 99 percent of treatment group received full loading dose, and 83 percent completed 24 hours of treatment at least.

The results of CRASH was astounding, the investigator initially thought corticosteroids would reduce the risk of death by 15 percent, but in contrary, the opposite occurred individuals who were treated with corticosteroids were 18 percent more likely to die with 14 days of their injury hence the trial was halted halfway. The CRASH investigators initially planned to enrol 20, 000 patients but stopped because of prior interim analysis of significant mortality at two weeks (21% versus 17%, P=0.0001). Twenty-one percent (1,052) of patients out of total 5,007 patients who received methylprednisolone died within 14 days of being injured. In comparison, 893 patients (19.9 percent) out of 5,001 patients who received placebos died. Subsequent follow up demonstrated that six months' mortality was higher in corticosteroid treatment group (25.7% versus 22.3%, P=0.0001). There was no difference in the result regarding injury severity or time

since injury in both initial and follow up study. Hence Corticosteroid (methylprednisolone) increase mortality in the two weeks after head injury. The cause of the rise in risk of death two weeks after head injury is unclear. The authors did not include the cause of death data and by implication, therefore, found an only association between steroid treatment and higher mortality rates, not a causal relationship. The main question this study did not answer or reveal is why corticosteroid-treated patients fare worse compared with placebo-treated patients. Complications such as gastrointestinal bleeding, infection and seizures were synonymous to both groups. Also, the mechanism that led to this finding was inexplicable coupled with lack of identifiable aetiology diminished the validity and importance of this study.

Before the CRASH study, corticosteroid was also tried in spinal cord trauma. US National Acute Spinal Cord Injuries Studies (NASCIS-2 and NASCIS-3) showed that short-term, high dose corticosteroids might improve neural recovery [14].The authors of CRASH did not report the percentage of patients with combined traumatic head and spinal injury leaving open to argument whether patients with combined head and spinal cord injury should receive steroids.

By this study and data corticosteroid use in the treatment of acute traumatic brain injury was not only deemed useless but even dangerous. Hence, for now, corticosteroids should not be used routinely to treat acute traumatic brain injury until there are more robust evidence since firm proof are presently lacking in head trauma and still controversial in spinal trauma. This is a well-conducted randomised controlled trial, and this will be assigned 1- in the hierarchy of evidence (Appendix 1).

Marshal et al. [21] conducted a multicentre trial on the efficacy of using tirilazad mesylate in cases of head injury. The significant recognition of the importance of lipid peroxidation as an experimental process led to the development of neuroprotective agents having the inherent ability to ameliorate secondary insults associated with traumatic brain injury. One of the drugs in this class is tirilazad mesylate, a novel 21-aminosteroid derivative with proven antioxidant effect. The efficacy of this drug has been demonstrated in a various model of experimental brain injury. The objective of this study is to evaluate the efficacy of tirilazad mesylate in human with head injuries. This is a large prospective, double-blind placebo-controlled international RCT in moderate and severe head injury.

This study randomised 1,131 patients of which 1120 received at least one dose of the study medication, either tirilazad or placebo. Eighty-five percent (957) had suffered severe head injury (GCS score 4-8) while 15% (163) sustained a moderate head injury (GCS score 9-12). Both groups of drug and placebo showed good recovery but no significant difference after six months

This study could not demonstrate the efficacy and benefit of the use of tirilazad mesylate in patients with severe and moderate head injury, but a potential positive effect may exist in male patients with traumatic subarachnoid haemorrhage due to a head injury. However, a positive outcome of this study is the demonstration and promotion of strong international collaboration and understanding for the ultimate benefit of patients. This is a good sign for future research.

Overall this is a well-conducted randomised control trial though the cost economics is omitted. This study would be level 1+ in the hierarchy of evidence through the result cannot apply to the local setting and population.

Grumme et al. [13] carried out a prospective controlled multicentre trial on the treatment of severe head injury with triamcinolone. This study aims to ascertain the outcome of severe head injury following treatment with synthetic corticosteroid triamcinolone. This is a double-blind trial where 386 patients were randomised to steroid group consisting of 187 patients who received 200mg triamcinolone acetonide intravenously within four hours after trauma; subsequent reducing doses followed this. The placebo group was subjected to same standard treatment procedure. Despite firm inclusion and exclusion criteria, the population in study remain heterogeneous consisting of patients with huge variety of mechanism of damage, pathology and clinical condition. Randomization should result in an even distribution of these factors between placebos and treated group, this goes a long way to influence the ultimate result regarding robust design, and these factors are potential co-founder that can influence the outcome. A sample size of approximately 800 to 1000 patients is considered significant for a trial in a population of patients with severe traumatic brain injuries. The sample size is too small to ensure detection of clinically significant effect hence this can lead to an imbalance in the outcome. Imbalances can be reduced by appropriate stratification in randomisation, apart from the treatment and control group, a subgroup was created on account of GCS hence triamcinolone has shown to be beneficial in patients with a severe head injury less than 8.

The result of treatment with triamcinolone was assessed at discharge from the hospital one year after traumatic brain injury using the Glasgow Outcome Scale. More patients with steroid had good recover (49.2% versus 40%), and fewer died (16.0% versus 21.5%). This was more pronounced in outcome difference in patients with focal lesion and a Glasgow Coma Scale of less than 8 on admission (p= 0.0145), in this group of patient 34.8% made a good recovery as against 21.3% as against 21.3% of the placebo group, also low mortality in this group of patient. The statistical techniques used are mostly discriminant analysis or logistic regression analysis which was virtually absent in this study thereby reducing the internal validity.

The result indicates that a significant subgroup of patients with traumatic brain injury will benefit from triamcinolone. Efficacy of treatment can be expected in patients with a focal cerebral lesion like supratentorial contusion; and low Glasgow Coma Scale of less than eight on admission, also the administration of steroid will also be beneficial if given from the beginning of the scene of the accident.

Identification of those patients with head injury in whom the therapeutic effect of corticosteroids is most probably remains a significant problem. Although some authors are still convinced that corticosteroids have a positive effect on a subgroup of patients with severe head injury while others no longer recommend administration of corticosteroid in the management of acute traumatic brain injury.

Given the heterogeneous nature of the head injury, a targeted population with high morbidity and mortality rate may be more suitable for a clinical trial of this agent. In summary, this is level 1— evidence has some inconsistencies in its methodology.

Dearden et al. [12] conducted a randomised controlled study on the effect of high-dose dexamethasone on outcome from severe head injury. This is said to be based on the traditional value of steroid administration in reducing cerebral oedema associated with a brain tumour[3] and also the influence of high-dose steroids on raised intracranial pressure and its conflicting evidence. This answered a very question with regards to the effect of corticosteroid on traumatic brain injury. It adds further evi-

dence on the problems with the side effects with this treatment regimen. g This study is synonymous to that of Braakman et al. [14] regarding the duration of assisted ventilation and intensive care between steroids, and placebo groups showed that the incidence of severe infection was not different significantly between the two groups. Also regarding design and number of patients and this confirms their conclusion that high dose dexamethasone is of no benefit following severe head injury. Hence based on this study one can say that administration of glucocorticoids is no longer indicated in the management of traumatic brain injury even in the face of elevated intracranial pressure (ICP).

This study is poorly conducted with low internal validity and low rigour and high risk of bias. It can be classified as 1- study on the hierarchy of evidence.[20] [Appendix 1]

Braakman et al. (1983) conducted a prospective, double-blind clinical trial of the effectiveness of high –dose steroids in head-injured patients who were in a coma on admission. This study benefited from a very robust study protocol with clear focus with well laid out inclusion and exclusion criteria. The methods of patient's assessment confirmed to known standard with the use of Glasgow coma scale, strict adherence to the indication for the insertion of intracranial pressure monitor, however, one of the centres involved in this study had more patients artificially ventilated, and ICP monitored.

Patients were randomised into two groups a placebo group and a high-dose dexamethasone group with an initial dose of dexamethasone 100mg/day intravenously or intramuscularly days 1 to day 4, 16mg/day for days 5 to 7and 8mg/day for days 8, 9, ten respectively. Survival at one month was taken as the measure of the effectiveness of high dose steroid. The number of deaths in the placebo group was slightly higher than the steroid group. More importantly, this study did investigate the effect of steroid or placebo on intracranial pressure (ICP) even when all patients had intracranial pressure monitor in place. This study is a poorly conducted study with low internal validity and rigour, and high risk of bias, it can be classified as a level 1- study on the hierarchy of evidence to support the author's conclusion on the effect of mega-dose steroid on head injury[20] [Appendix 1]

Corticosteroid used in the management of acute traumatic brain injury have included dexamethasone, methylprednisolone, betamethasone, cortisone, hydrocortisone, triamcinolone, also in this group will be progesterone and tirilazad mesylate an aminosteroid. The use of these myriads and variety of steroid component and composition have complicated sound and adequate understanding of corticosteroid efficacy in the management of traumatic brain injury; this has been exacerbated by a lack of knowledge of the mode of action of steroid in this setting. There has been evidence from experimental laboratory studies of reduction in wet brain weight, lipid peroxidation, and enhanced blood flow and membrane stabilisation with corticosteroid use. In the light of series of inconclusive evidence into the efficacy and safety of corticosteroid use in severe head injury, an extensive multinational randomised collaboration for assessment of early methylprednisolone administration was initiated in 1991 (Roberts et al., 1999). To achieve 90% power, 20,000 patients were to be recruited in the Corticosteroids Randomization after Severe Head Injury (CRASH) trial as the initial goal.

The CRASH trial which has become the definitive study of corticosteroid till date and also the largest randomised placebo-controlled multicentre trial of early steroids in 10,008 adults with a head injury. This well-designed research was remarkable because of the logistics of conducting a blinded trial in 239 hospitals across 49 countries with 96.7% six months follow up however the trial was halted when the interim analysis showed that steroid subject had significantly higher all two weeks mortality. Similarly, six months follow up demonstrated high mortality in steroid patient. Based on the results of huge and robust study, the CRASH trial, steroids should not be used routinely in the treatment of acute traumatic brain injury however the authors remained unsure of the mechanism of increased mortality with steroids. Before the CRASH trial a 0.96 (95% CI 0.85-1.08) relative risk of death was reported in the corticosteroid group, but when the CRASH trial was included in the meta-analysis performed by Roberts et al., its relative risk was increased to 1.12 (95% CI 1.05-1.2) by CRASH trial.

In the included studies in this review, methylprednisolone use was assessed by two studies, and both reported no positive improvement in GOS outcome at six months. Based on the results of this extensive multinational trial, the study authors concluded that corticosteroid should not be used in head injury irrespective of the severity of the head injury.

Grumme et al. (1995) is the only study that reported a positive result that synthetic corticosteroid triamcinolone improved outcomes in patients with both GCS less than 8 and a focal lesion. This Randomised Controlled Trial was conducted in Germany and Austria in which GOS scores were assessed in patients after one year with treatment with a synthetic corticosteroid, triamcinolone.

Dearden et al. (1986) and Brackman et al. (1983) randomised controlled trials assessed use of dexamethasone in acute traumatic brain injury. Patients with ICP levels greater than 20mmHg were noticed to show significantly poorer outcomes evidenced by six months GOS scores. A study by Brackman et al. showed no significant differences between patients treated with dexamethasone in comparison to those treated with placebos in one-month survival or six-month GOS scores.

Currently, no pharmacologic agent has been shown to improve the outcomes of traumatic brain injury significantly. Methylprednisolone taught to carry the potential for good treatment but found to be harmful in traumatic brain injury. The recent large-scale trial of magnesium was disappointing. However, progesterone has emerged as a promising therapeutic option. Progesterone has been identified as a potential neuroprotective. This has been identified as a potential neuroprotective agent, Animal research has shown possible effect of progesterone to modulate excite-toxicity, reconstitutes the blood-brain barrier, reduces cerebral oedema, regulates inflammation and decreases apoptosis [15]. Progesterone has several significant features that make it an attractive potential drug for treatment of acute traumatic brain injury. Progesterone could protect against brain damage (neuroprotective agent). The pharmacokinetics of progesterone and its adverse effect pattern are well known since it been in use for a long time [16]. Also, there is a wide therapeutic window of progesterone, a single bolus given up to 24 hours post injury may significantly reduce cerebral oedema [17]. Also, progesterone may rapidly cross the blood-brain barrier and reach equilibrium with the plasma within one hour of administration [18]. There is significant possibility that administration of progesterone soon after traumatic brain injury would probably benefit the recovery of the patient.

Only two clinical studies on progesterone use in traumatic brain injury have been published. Wright et al. assessed progesterone versus placebo results demonstrated no increase in complication rate and a decrease in 30-day mortality in the pro-

gesterone group. Study by Wright et al. [10] outcome analysis suggests but does not prove that progesterone causes no harms and may be a beneficial treatment tool for traumatic brain injury, however, a more extensive trial involving multinational collaboration involving multiple clinical sites, 1:1 randomisation and rapid initiation of treatment is warranted.

CONCLUSION

There is Level 1 evidence that Methylprednisolone increases mortality rates in acute traumatic brain injury patients and should not be used. There is a level 2 evidence that triamcinolone may improve outcomes in patients with a GCS less than 8 and a focal lesion. There is a level 1 evidence that dexamethasone does not improve ICP levels and may worsen outcomes in patients with ICP greater than 20mmHg.There is a level 2 evidence that progesterone can improve neurologic outcomes for up to 6 months in acute severe traumatic brain injury patients.

Appendix 1 (Grading Tool)

A new system for grading recommendations in evidence-based guidelines Harbour, R. and Miller, J. 2001. The Scottish Intercollegiate Guidelines Network Grading Review Group. Scottish Intercollegiate Guidelines Network, Royal College of Physicians of Edinburgh, Edinburgh EH2 1JQ Levels of evidence

1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or High-quality case-control or Cohort studies with a very low risk of confounding bias, or chance and a high probability that the Relationship is causal.

2+ Well-conducted case-control or cohort studies with a low risk of confounding bias, or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3 Non-analytic studies, e.g. case reports, case series

4 Expert opinion.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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