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A Case of Severe Postoperative Agitation and Literature Review

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1. Abstract

Postoperative agitation in adults is a common occurrence during the recovery period after anesthesia. It can lead to serious injuries for both the patients themselves and the medical care team. Unlike delirium, agitation is a self-limited clinical condition in which patients regain consciousness. However, the current literature on postoperative agitation in adults is relatively scarce compared to that in children, and it is limited to small-scale clinical studies that use inconsistent evaluation scales, definitions, and time points. As a result, the reported incidence rates vary widely.

The proposed mechanisms for postoperative agitation in adults are still theoretical and lack a consensus among researchers. Although many risk factors have been identified, most of them are unavoidable, and even targeted treatments such as pain relief sometimes prove to be ineffective, suggesting that these factors do not play an independent role. Preventive strategies and management techniques focus on eliminating risk factors and addressing harmful behaviors. Pharmacological strategies primarily involve the use of anesthetics and analgesics, including propofol, ketamine, dexmedetomidine, and others. However, there is still controversy surrounding the use of these drugs, as factors such as delivery time, route, and dosage may influence their efficacy. Non-pharmacological strategies also warrant further attention and research, as medications can prolong recovery time and post-anesthesia care unit (PACU) stay.

In this article, we present a case study that highlights a unique risk factor and treatment method, aiming to explore additional possibilities for managing postoperative agitation. We also provide a comprehensive summary of the current knowledge on adult postoperative agitation, covering definitions, evaluation tools, risk factors, mechanisms, preventive strategies, and management techniques. Furthermore, we analyze the current research trends and status in this field to encourage further exploration.

2. Introduction

Postoperative agitation is a common occurrence during the recovery period following anesthesia and can result in physical injuries to both patients and the healthcare team, as well as other serious consequences such as increased hemorrhage, pain, and removal of catheters and tubes [1, 2]. A significant portion of postoperative agitation may manifest as postoperative delirium from the time of emergence until discharge from the post-anesthesia care unit (PACU) [3]. This can lead to prolonged hospital stays, increased economic costs, and even mortality [4]. Moreover, early postoperative delirium in the PACU has been found to be predictive of subsequent delirium after surgery and is associated with worse outcomes [3, 5].

The incidence of postoperative agitation in adult patients is reported to range from 5% to 30%, varying due to factors such as age distribution and assessment scales [6]. Additionally, the incidence varies greatly among different types of surgeries [7-9]. However, there is still a lack of consensus regarding the diagnostic criteria and accurate definition of this complex condition [10]. Treating

agitation is also challenging and complex due to its heterogeneous etiology, variations in patient status, and difficulties in integrating guidelines or recommendations into clear and implementable protocols [3]. Furthermore, agitation in adults is less frequently observed and studied compared to children, necessitating further research. In this report, we present a unique case of agitation during emergence and provide a summary of relevant research to deepen our understanding of this symptom.

3. Case Presentation

A 63-year-old man, scheduled for selective laparoscopic radical gastrectomy, was admitted to our hospital on July 23rd. He had no significant medical history, and all relevant preoperative examinations, except for tumor markers and chest radiography showing bronchiolitis in both lungs, were within the normal range. Physical examination revealed no positive signs, including abnormalities in cardiopulmonary auscultation.

Following preoperative preparation, the patient underwent surgery on the morning of July 26th under general anesthesia combined with regional nerve block. The day before the surgery, his family members were informed about the potential risks associated with the peri- and post-anesthesia period, including pain, postoperative nausea and vomiting (PONV), delirium, agitation, and other complications. Informed consent was obtained and signed.

No premedication was administered on the day of surgery. Dexmedetomidine was infused at a rate of 50μg/h based on the patient's body weight of 60kg for 40 minutes, immediately upon the patient's admission to the operating room. Anesthesia induction was performed using midazolam 2mg, fentanyl 0.15mg, propofol 10mg, cisatracurium 16mg, 1% lidocaine 5ml, tropisetron 10mg, and dexamethasone 5mg. Ultrasound-guided bilateral rectus sheath nerve block was performed using a mixture of 20ml 1% lidocaine and 0.375% ropivacaine. Tracheal intubation was successfully carried out, and the depth of the tube placement was appropriate as confirmed by auscultation. Prior to the surgery, invasive procedures such as radial artery cannulation, internal jugular vein catheterization, gastric tube insertion, and indwelling catheter placement were performed smoothly without any additional injuries.

The surgery lasted for 2 hours, during which anesthesia was maintained with 1% sevoflurane, 1% propofol at a rate of 10ml/h, remifentanil at 0.5mg/h, and cisatracurium at 6mg/h before closing the abdomen. Due to the complexity of the operation, moderate to severe surgical exploration was performed by the surgeons, resulting in the extension of the surgical incision. After tumor resection, two drainage tubes, a jejunal nutrition tube, and a gastric tube were placed. For pain control, an additional 8μg of sufentanil was administered before exploring the abdominal cavity, and 40mg of parecoxib was given at the time of closing the abdomen.

Hemodynamics remained relatively stable throughout the surgery, with the lowest mean arterial pressure (MAP) recorded at 76mmHg and the highest at 119mmHg during extubation. Other vital signs, including heart rate, SpO2, ETCO2, arterial blood gas (ABG), and urine volume, remained within normal ranges, except for a nasopharyngeal temperature of 35.5°C at the end of the surgery.

After extubation, the patient vaguely complained of pain and was unable to specify the painful areas. Soon after, he developed dysphoria, constantly attempted to roll over, and waved his arms. In response, we immediately administered 5μg of sufentanil through the central venous line and attempted to communicate with him, intervening to prevent him from engaging in harmful actions when necessary. The patient could occasionally provide correct answers to questions about his personal information and orientation, but most of the time, he was in an uncontrollable state of agitation, scoring 6 points on the Richmond Agitation-Sedation Scale (RASS). To prevent self-injury and ensure the safety of the patient and healthcare staff, we administered 10ml of 1% propofol and restrained his activity using hand and foot straps. Subsequently, he was transferred to the Post-Anesthesia Care Unit (PACU).

In the PACU, the patient received intermittent injections of 5-10ml of propofol, and the Richmond Agitation-Sedation Scale (RASS) score was assessed once the sedative effect wore off. However, after 40 minutes, there was no improvement observed. We then decided to try dexmedetomidine nasal drops at a dose of 100μg. Unfortunately, this intervention also showed no effectiveness in calming the patient. Subsequently, we administered dexmedetomidine intravenously at a rate of 60μg/h for 15 minutes, but still did not observe any positive response.

Given the persistent agitation and lack of response to conventional measures, we decided to discuss the patient's worrisome condition and the possibility of transferring him to the Intensive Care Unit (ICU) for further treatment with his family members. His family expressed their understanding of the situation and their willingness to accompany him. They were admitted to the PACU, and all intravenous drug administrations were discontinued. The RASS score was recorded every 10 minutes during this period.

Surprisingly, approximately 15 minutes after being joined by his family, the patient recognized them and gradually became calmer. The RASS score was evaluated to be 4 points, indicating a significant improvement. All the recorded scores are presented in Figure 1.

After spending 1.5 hours in the PACU, the patient was deemed stable and subsequently transferred to the medical ward. Follow-up assessments were conducted at 4, 12, 24, and 48 hours after the surgery, and no signs of agitation, delirium, or other complications were observed. Additionally, during further consultations at half a month, one month, and two months after being discharged from the hospital, there were no reported positive manifestations or complaints of discomfort from the patient or his family.

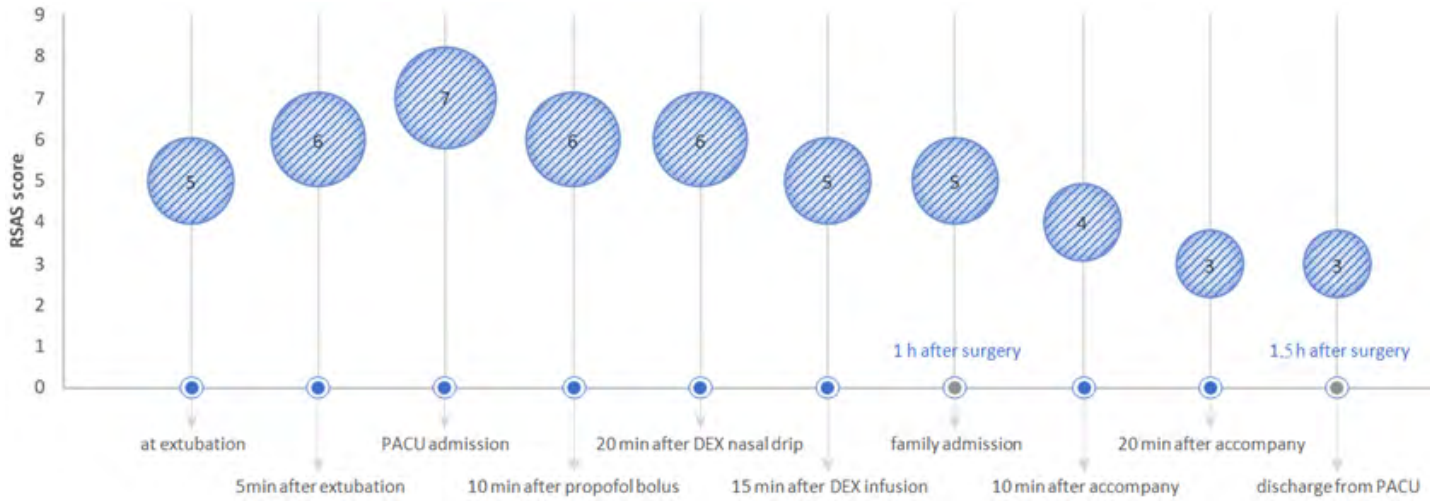

Figure 1: RSAS score of this agitated paitient at various time point.

4. Discussion

Although short-lived, postoperative agitation should not be ignored due to its great possibility of causing serious consequences. Moreover, the occurrence rates were not rare, especially in some special types of surgery as reported.

4.1. Definition

To data, there is no uniformly accepted definition of agitation, which brings many obstacles to researchers. Different from postoperative delirium, agitation at emergence or postoperative period represents a clinical entity [11], accurate definition and diagnosis are necessarily required. In 2016, 1st International Experts' Meeting on Agitation was convened in Madrid and there agitation was explicitly defined. Four specific signs were raised to help preliminarily identifying agitation: 1) Inability to stay still or calm; 2) Internal features such as hyperresponsiveness, racing thoughts, emotional tension; 3) external features mainly refer to motor and verbal hyperactivity; 4) communication impairment [10]. Besides, many researches described postoperative agitation as a state of confusion, disorientation together with purposeless or aggressive behaviors [6, 7, 9, 12, 13], unawareness of surroundings [11]. In children, they might be inconsolable and absence of eye contact with caregivers [14]. Although lack of golden standard, many assessment tools were widely accepted and adopted in clinical practice and research, also they presented good applicability and reliability. Richmond Agitation-Sedation Scale(RASS) [15] and Riker Sedation-Agitation Scale(RSAS, in some study abbreviated as SAS) [16] were the most frequently used tools, good consistency between the two was displayed in various studies. While there were still other scales including modified Pediatric Anesthesia Emergence Delirium(PAED) scale [17], Emergence Agitation Score [18] and Aono's 4 point scale [19] for adult. Variety characteristics and evaluation methods suggest no uniform standards for agitation, much effort still need to further explore this field.

4.2. Incidence

In adult patients, the incidence of postoperative agitation was diverse, which were affected by age, gender, types of surgery and many other factors. We reviewed some clinical studies in recent 11 years and summarized the occurrence rates under different situations in Table 1.

In general, nasal surgery is the most frequently studied surgery type, with the incidence of agitation ranging from 20% to 54% [7, 20-27]. Agitation in orthognathic surgery is also well explored and the reported incidence varies from 47% to 71% [28-30]. Other types of surgery including thoracic, abdominal, thyroid, craniocerebral [8, 31, 32], urological surgery [33], cesarean section [34] and outpatient intravenous general anesthesia [35] reported wide range of occurrence of agitation, that might due to methodological differences and lack of consensus on definition and diagnosis as mentioned above. Except for the type of surgery, selection of assessment tools, premedication and anesthesia induction and maintenance technique should also be considered as important confounding factors. We summarized the observed incidences of agitation in some related researches and listed in Table 1 for reference.

Table 1: Occurrence rates of postoperative agitation under different situations.

Year	Authors	study type	feature	incidence		surgery type	asseessment tool	intervention/control
				intervention group	control group			
2019	Hoon Choi et.al	RCT	EA	20.00%	62.50%	septorhinoplasty	SAS	never block/sham
2019	Lee et al.	retrospective study	EA	26.90%	50.80%	nasal surgery	RASS RSAS	tramadol/no tramadol
2019	Kang et al.	retrospective study	EA	10.90%	15.00%	lung surgery	RSAS	dexmedetomidine/no dexmedetomidine
2019	João Manoel Silva-Jr et al.	RCT	psychomotor agitation	1.00%	15.00%	unlimited	RASS	dexmedetomidine/midazolam
2019	Jong Chan Kim et al.	RCT	EA	8.00%	18.00%	closed reduction of a nasal bone fracture	Aono's 4 point scale	dexmedetomidine/saline

2018	Huang H-W et.al	prospective cohort study	PA	13.00%		craniotomy for brain tumors	SAS	/
2018	Jun-Young Jo et.al	randomized clincal trail	EA	2.50%(RSAS RASS)	25.00%(RASA)	nasal surgery	RSAS RASS	TIVA/VIMA
2018	Kim et al.	RCT	EA	13.00%	35%	elective video-assisted thoracoscopic lobectomy/ segmentectomy	RSAS	dexmedetomidine/no dexmedetomidine
2018	Fields et al.	retrospective study	agitation in PACU	0.25%		unlimited	RASS	/
2018	Rodrigues HF et al.	obsverational analytical study	agitation in ICU	17.30%		CABG	Not described	/
2018	DEHUA KONG et al.	RCT	PA	0.00%	11.76%	cesarean section	Not described	dexmedetomidine/morphine
2018	Canser Yilmaz Demir et al.	RCT	EA	28.60%	54.30%	Rhinoplasty	RASS	ketamin/saline
2017	Hazem E. Elsersy et.al	RCT	agitation in PACU	59.00%	74%	endoscopic sinus surgery	RASS	magnesium sulphate/saline
2017	Jee et al.	RCT	EA	34.00%	54.00%	nasal surgery	RASS	nefopam/saline
2017	Hyun-Jung SHIN et al.	retrospective study	PA	2.30%	6.50%	orthopedic surgery	RASS	dexmedetomidine/propofol
2017	Marie T. Aouad et al.	RCT	EA	33.00%	72.00%	unlimited	6 point scale	dexmedetomidine/saline
2016	liang lin et al.	comparative study	EA	6.00%	24.00%	gastric cancer	customized	combined premedication of butorphanol and ketamin/single use
2015	Geng et al.	RCT	EA	not reported		tangential excision surgery	customized	flurbiprofen combinde with sufentanil
2015	R. Polat et al.	RCT	EA	3.3% in group R, 20% in group D	46.70%	nasal surgery	RSAS	remifentanil(R)/ dexmedetomidine(D)/saline
2015	G. J. Choi et al.	RCT	EA	24.00%	71.00%	orthognathic surgery	4 grade based on Aono's scale	desflurane/sevoflurane
2015	Hyo-Jin Kim et al.	retrospective study	EA	22.20%		nasal Surgery	RASS	/
2014	Kim et al.	retrospective study	EA	10.00%		urological surgery	RSAS	/
2014	S. Y. Ham et al.	RCT	EA	38.00%	47.00%	orthognathic surgery	RASS	dexmedetomidine/saline
2014	Lu Chen et al.	prospective cohort study	EA	29.00%		elective craniotomy for brain tumors	SAS	/
2013	Kim et al.	RCT	EA	52.00%	28.00%	nasal surgery	RSAS	dexmedetomidine/saline
2010	Yu et al.	prospective observational stud	EA	21.30%		unlimited	customized	/

Abbreviations: SAS: sedation-agitation scale; RASS: Richmond Agitation-Sedation Scale; RSAS: Riker sedation-agitation score; PA: postoperative agitation; EA: emergence agitation; RCT: randomized controlled trail.

4.3. Risk Factors

Numerous risk factors were reported to be closely related with agitation, however, none of them had been proven to be pathogenetic issue. Well-known risk factors of agitation include postoperative pain [25, 36], presence of endotracheal especially prolonged mechanical ventilation [37, 38], and/or indwelling catheter [1, 39], younger or older age [40, 41], ASA I physical status [26], male sex [32, 36], current smoking [26, 27]. Among them, postoperative pain, catheter(including tracheal, gastric and urinary tube), longer anesthesia and surgery duration [32], together with chronic lung disease, history of social drinking, voiding urgency [33], history of long-term treatment by anti-depressant agents [32] and pneumocephalus [8] were identified as independent risk factors for agitation.

In children, use of inhalation anesthetics, especially sevoflurane [42], in general anesthesia were long considered to be closely associated with high incidence of agitation in emergence and postoperative period [43], while Wei et al. [44] analyzed that inhalation anesthesia also influence adult emergence agitation (EA), although sensitivity analysis of omitting study of Kim [27] or Wiinholdt [45] did not support this conclusion; of three common inhalation anesthetics including sevoflurane, desflurane and isoflurane, desflurane anaesthesia presented less EA and superior cognitive functions compared with sevoflurane and isoflurane anaesthesia [29, 46, 47]. Precious few research focused on the effect of isoflurane anaesthesia on agitation. In general, most study consider total intravenous anaesthesia (TIVA) is superior to volatile induction/maintenance anaesthesia (VIMA) in preventing postoperative agitation [20, 37, 42, 48]. Solid evidence for choosing anesthesia method of relatively low risk of EA has guiding significance for clinical work in situation where other risk factors seem inevitable.

It is noteworthy that several studies [20, 21, 23, 27] reported nasal packing, which would cause suffocation on emergence, actually was not a risk factor for postoperative agitation in spite of high incidence in nasal surgery. Nevertheless, postoperative pain seemed not to induce agitation itself, as Elsersy et.al [49] found reduction of pain in patients undergoing functional endoscopic surgery was independent of reduced agitation, and painless procedure [22, 27, 41, 50] could also induce agitation, indicating confounding factors existed, and further study is needed to further explore this subject.

In this case, the occurrence of agitation might be related with the following elements: 1) too many tubes existing; 2) postoperative pain, despite the administration of never block in advance and parecoxib sodium 30min before the end of surgery; 3) vigorous surgical exploration, which was a very special issue to this patient. We searched this topic in adult patient undergoing abdominal surgery and no related hints had been found. Then we observed several similar surgeries in our hospital, when surgical exploration was performed much more severe, the incidence of agitation seemed

higher, but in that situation, more tubes were also placed. We cannot tell this special issue is correlated with postoperative agitation without rigorous randomized controlled studies and analysis.

4.4. Mechanism

The pathophysiological mechanisms underlying postoperative agitation are still largely unknown. Possible explanation could be the following.

Psychiatrists consider agitation is closely associated with an underlying psychiatric disorder [10, 51, 52], while several studies [9, 26, 29, 36, 37, 53] also found that preoperative anxiety in adults was positively correlated with agitation, Fields et al. [1] proved that preoperative cognitive impairment and psychiatric disorders were associated with the development of agitation. Preoperative depression [54, 55], use of preoperative anti-depressant drugs or benzodiazepines [32] were also proved to be strongly correlated. Many studies [56-58] evaluated the correlation between preoperative mental health status and postoperative characteristics, and few or no were focused on agitation.

N-methyl-D-aspartic acid (NMDA) receptor has long been considered to relate with EA, although underlying mechanism had not been elaborated. Animal experiments found NMDA receptor GluRε1 subunit knockout could result in locomotor hyperactivity in a novel environment upon emergence from sevoflurane inhalation anesthesia, while wild type did not [59]. Acute inhibition of 14-3-3 family proteins through delivery of adeno-associated virus (AAV) into hippocampus, which was demonstrated to regulate postsynaptic NMDA receptor levels, could induce several behavioral deficits including hyperactivity and reduced sensorimotor gating [60]. McLott et.al assumed that NMDA postsynaptic potential induced excitatory hyperactivity at thalamolateral nucleus of amygdala synapse enhaced the uncomfortable stimuli-induced behavior [61], and NMDA receptor antagonists including ketamine [26, 62], magnesium sulfate[49], tramadol [23] and nefopam [22] showed obvious preventive effects on postoperative agitation in clinical tests. However, despite the direct activation of NMDA receptor, infusion of remifentanil was been proved to decrease the incidence of EA with a smooth awakening [25, 63]. Some scholars hypothesize potent analgesia is more important on reducing agitation than prevention of NMDA receptor [22], which need to be further testified.

The most widely known hypothesis of agitation in children might be the different recovery rates of inhalation anesthetics from the central nervous system, where locomotion and audition recover first, followed by cognitive function [64, 65]. This might due to the different solubility, which was consistent with the relative higher incidence of agitation in desflurane anesthesia with lower blood-gas partition coefficient (0.42) compared with sevoflurane(0.69) [66], although some studies reported no differences between the two of them. In adults, the situation seemed distinct. Choi et al. [29], found a lower incidence of EA in desflurane anesthesia compared with sevoflurane, this might attribute to rapid recognition of surroundings and a greater sense of control since a significantly faster emergence of desflurane anesthesia. Other studies also support this finding as mentioned above.

4.5. Prevention

A great many studies have focused on the prevention strategies to reduce postoperative agitation. We reviewed related literature and summarized at below. Generally we classified them into pharmacological and non-pharmacological methods.

4.5.1. Pharmacological Strategies

4.5.1.1. Inhalation anesthetics: Studies tend to consider that desflurane is superior than sevoflurane on reducing postoperative agitation in adults[29, 46, 47]. Nevertheless, clinically we can choose TIVA or balanced anesthesia instead of VIMA, taking into account the prevention of agitation. In two randomized controlled trails (RCTs), patients undergoing TIVA or balanced anesthesia (sevoflurane and sufentanil, sevoflurane and propofol combined maintenance, respectively) showed nondistinctive incidence of agitation in laparoscopic cholecystectomy[67] or modified radical mastectomy surgery[68]. Similar conclusion in a multicenter RCTs of adult patient undergoing elective craniotomy was reached either[69]. In children, transition to propofol[70-72], administration of small dose of ketamine or nalbuphine[73] just before discontinuing sevoflurane anesthesia led to significant decrease of EA, which might be a meaningful hint for adult patient.

4.5.2. Intravenous anesthetics

4.5.2.1. Propofol: As a maintenance drug for TIVA and balanced anesthesia, propofol presented a significant effect on reducing the incidence of postoperative agitation, administration of propofol instead of sevoflurane before the end of the surgery also showed demonstrable effectiveness in children, which provides a clear indication for clinical anesthesia. Still, transition to propofol maintenance in inhalation or balanced anesthesia to prevent postoperative agitation in adult patient has not been proved to be effective, related research is needed.

4.5.2.2. Benzodiazepines: Use of benzodiazepines as premedication or during the operation or just before the end of surgery presented controversial effect on agitation in children and adults. When used preoperatively, benzodiazepines seemed to increase the risk of agitation in PACU[2, 27, 41], Wei et al.[44] considered that intraoperative use of benzodiazepines to be possible risk factors for adult EA, similar with this conclusion, intraoperative sedation in elderly patients with midazolam showed higher psychomotor agitation than with dexmedetomidine[74], while in another research which focused on prevention of EA after nasal surgery, effect of intravenous infusion of midazolam and dexmedetomidine exhibited comparable, except for more severe and a longer duration of agitation in midazolam group [13].

Effect of midazolam administration at the end of surgery on emer-

gence agitation in children[75, 76]who were anesthetized with sevoflurane was comparable with propofol, while in adults we didn't found related research.

4.5.2.3. Opioids: As the main analgesics in general anesthesia, opioids were thought to effectively reduce EA, however, related research was rare in adults. Polat et.al [25] found that continuous infusion of remifentanil during nasal surgery showed superior effect on reducing EA compared with infusion of dexmedetomidine, while Kavalci et al. [77] considered an equal effect of remifentanil and dexmedetomidine on EA in adults undergoing septoplasty operation. And many studies agreed that combination with dexmedetomidine in general anesthesia with opioids, intravenous or inhalation anesthetics both in children [78-81] and adults [82, 83] had a potential effect on decreasing postoperative agitation compared with control groups, which provided meaningful reference for clinical medication.

4.5.2.4. Ketamine: In addition to being used for induction and maintenance of anesthesia, ketamine was widely used in the prehospital setting [84], emergency department [85, 86] and ICU [87], in patients undergoing mechanical ventilation[88, 89] and procedural sedation [90] for management of agitation, due to its unique properties including profound analgesia, NMDA receptor antagonism, rapid onset, multiple available routes of administration and "dissociative anesthesia". Perioperative use to prevent postoperative agitation was rarely reported. In one RCT which enrolled 140 adult patients who were scheduled for rhinoplasty, intravenous infusion of ketamine before surgery completion demonstrated a significant decrease of EA [26]. When combined injected with butorphanol before anesthesia induction, ketamine also showed remarkable preventive effect on EA [62]. However, some studies considered ketamine as a factor which could lead to recovery agitation after procedural sedation at emergence department [91], the incidence had been estimated to be approximately 15% to 68% in different trails [92, 93]. More studies are needed to confirm the definiteeffect of ketamine.

4.5.2.3. Non-Steroidal Anti-inflammatory Drugs (NSAIDs): Quite few studies reported the correlation between NSAIDs and postoperative agitation, one study on parecoxib in children [94] and two studies focusing on parecoxib sodium [95] and flurbiprofen axetil [18] in adults presented positive results, possibly due to their analgesic and anti-inflammatory effect.

4.5.2.4. Dexmedetomidine: As a specific α2-adrenergic receptor agonist, dexmedetomidine has been widely considered to effectively prevent postoperative agitation both in children and adults. Used as premedication before closed reduction of nasal bone fracture, dexmedetomidine reduced the incidence, severity and duration of emergence agitation [19]. Intraoperative infusion of dexmedetomidine during thoracic surgery [9, 96], nasal sugery [24, 25], orthopaedic surgery [30, 97] showed remarkable effect on decreasing postoperative agitation. Other administration methods including postoperative nasal drip [98], single bolus 5 minutes after anesthesia induction [99] also proved the preventive efficacy. Treatment of agitation in intensive care unit was reported either [100, 101]. However, Ham et al.[28] reported that single intravenous infusion of dexmedetomidine for 10 minutes at the end of orthognathic surgery did not reduce EA, despite lower pain score and faster recovery phase; persist infusion of dexmedetomidine and remifentanil during microvascular free flap surgery showed similar incidence of EA, although agitation in PACU was less since use of dexmedetomidine [82]. In addition, a rare case presented infusion of dexmedetomidine at a small dose(0.5μg/kg) during procedural sedation, on the contrary, caused agitation, which possibly due to increased central sympathetic activities [102].

4.5.2.5. Other Analgesics: Other analgesics reported to alleviate postoperative agitation mainly included the following three: tramadol, pethidine and nefopam. Still few research paid attention to this topic especially in adults. Retrieved studies demonstrated that tramadol had an effect on reducing EA in nasal surgery[23], while it might be less effective than pethidine in children [103] and dexmedetomidine in adults[104] undergoing adenotonsillectomy. In traumatic brain injury patients, administration of tramadol, on the contrary, could more likely develop agitation in ICU[105]. Nefopam, as a NMDA receptor antagonist and analgesic, was reported to prevent and reduce the severity of EA after nasal surgery[22], as well as reduce the incidence and severity of catheter related bladder discomfort[106] which was a main risk factor for EA.

4.5.3. Other Medications

Magnesium sulfate is a non-competitive NMDA receptor antagonist with antinociceptive effect, and inhibits the influx of calcium ions. In functional endoscopic surgery [49] and esophageal carcinoma [107], continuous infusion of magnesium sulfate during the surgery was reported to reduce postoperative agitation compared with saline pumping in adults. This effect might be related with plasma concentration of magnesium ions which was considered to protect the brain from ischemia injury caused by hypotension or other contributing factors [108, 109].

Antiepileptic drugs(AEDs) were also commonly used as premedication for preoperative anxiety and postoperative pain, and studies reported the RASS or RSAS score was significantly decreased in gabapentin [110] or pregabalin [111, 112] premedication group in adults, accompanied with less rescue analgesics ,lower pain scores and longer recovery time in PACU. Whether AEDs could alleviate postoperative agitation still need further exploration.

4.5.4. Non-Pharmacological Strategy

4.5.1.1. Nerve Block: Ultrasound guided nerve block provides potential analgesic effect during and after various surgery and improve the quality of recovery, the consumption of opioids used for postoperative analgesia is also decreased. In cytoreductive surgery, septorhinoplasty, nasal surgery and video-assisted thoracoscopic surgery, combination with nerve block including bilateral

rectus sheath block [113], combined infraorbital and infratrochlear nerve block [21, 114], external nasal nerve block [115] and erector spinae plane block [116] showed significant preventive effect on postoperative agitation, which provide a meaningful reference for clinical anesthesia. However, central nervous system and cardiovascular toxicity of local anesthetics [117] should be taken seriously especially under combined general anesthesia.

4.5.1.2. Special Processing: Postoperative pneumocephalus (PP) had been reported to be an independent risk factor for postoperative agitation in several studies [8, 118, 119], and the incidence ranged from 22.5% [8] to 96% [120], preventive strategy, that is, appropriate closure of the dura, presented great significance for postoperative agitation.

4.5.1.3. Family Involvement

In children, family-centered behavioral preparation for surgery was proved to reduce anxiety and the incidence of EA [121, 122], preliminary support for the use of simulated family presence also decreased agitation in older hospitalized delirious patients [123]. For anesthesiologist, preoperative evaluation and harmonious communication with family members are of great importance. Family involvement in perioperative period showed advantageous on improving health outcomes of patients in bariatric surgery, although its influence on agitation had not yet been retrieved [124].

4.6. Management

Once occurred, should we take the initiative to deal with agitation? Some scholars considered EA as a self-limiting phenomenon lasting for a short period(1-15min) [125], elimination of causative factors such as pain [126] and urinary catheter [33] was the major management [36, 65]. However, long-lasting agitation after surgery still existed and could do great harm to patients themselves and medical care givers, physical restriction was necessary [127, 128]. Fields et.al [1] reported using of ketamine and midazolam for treatment of adult agitation in PACU, repeat dexmedetomidine loading [82, 129], propofol boluses [130] might also be useful to “smooth” reemergence. However, it should be noted that agitation itself is not a factor causing prolonged PACU stay, while sedative drugs are, whether, when and how to use is worthy of thinking.

In this case, preoperative communication with the family members made it possible to obtain understanding and support from the family after the occurrence of agitation, and the participation of family in PACU on the treatment of agitation achieved impressive effect. Whether family involvement is beneficial to the treatment of severe agitation needs further exploration.

4.7. Prospective

In order to provide more comprehensive understanding of this topic, we made a literature search with keywords including “postoperative agitation”, “emergence agitation”, “agitation and surgery” and bibliometric analysis, and drawn a bubble plot to demonstrate the trend and current situation. Totally 1164 publications on this topic were identified in pubmed from 1951 to 2021. Among them, Paediatric Anaesthesia was the journal with largest number of related publications (73 articles) from 1990 to 2021, followed by Anesthesia and Analgesia (43 articles), Acta Anaesthesiologica Scandinavica (27 articles), European Society of Anaesthesiology (21 articles) and others. Publications mainly distributed from 2002 to 2011, 2014 to 2019. Data were presented in Figure 2.

We also analyzed keywords and authors in retrieved research to recognize main concerns in this area. Keywords provided by authors of papers and occurred for more than 5 times in database were enrolled in the final analysis. Of the 2786 keywords, 369 meet the threshold. The keywords that appeared most frequent were “human” (total link strength 11102), “male”(total link strength 8528), “female”(total link strength 8087) and “child”(-total link strength 5046), they had a strong link to “psychomotor agitation” and “anesthesia recovery period” (Figure 3A). A word item density plot was also created to show the frequency of keywords (Figure 3B).Totally 5070 authors have participated in the publication of postoperative agitation articles. Among them, 21 scholars published more than 4 papers, while Terri Voepel-Lewis from University of Michigan Medical School in American has 7 papers mainly focused on pediatric agitation at emergence or in PACU. The main collaborators with him are Shobha Malviya and Alan R Tait both from University of Michigan Health Systems. The total link strength is 10 (Figure 3C). Of all authors, the number of organizations they come from is 1752, and 5 of them have over 3 publications. unfortunately, we did not find any correlation of these organizations, and the link strength was 0. Through this analysis, we hope to provide convenience for researchers who are interested in this filed, after all, much unknown remain need to be explored.

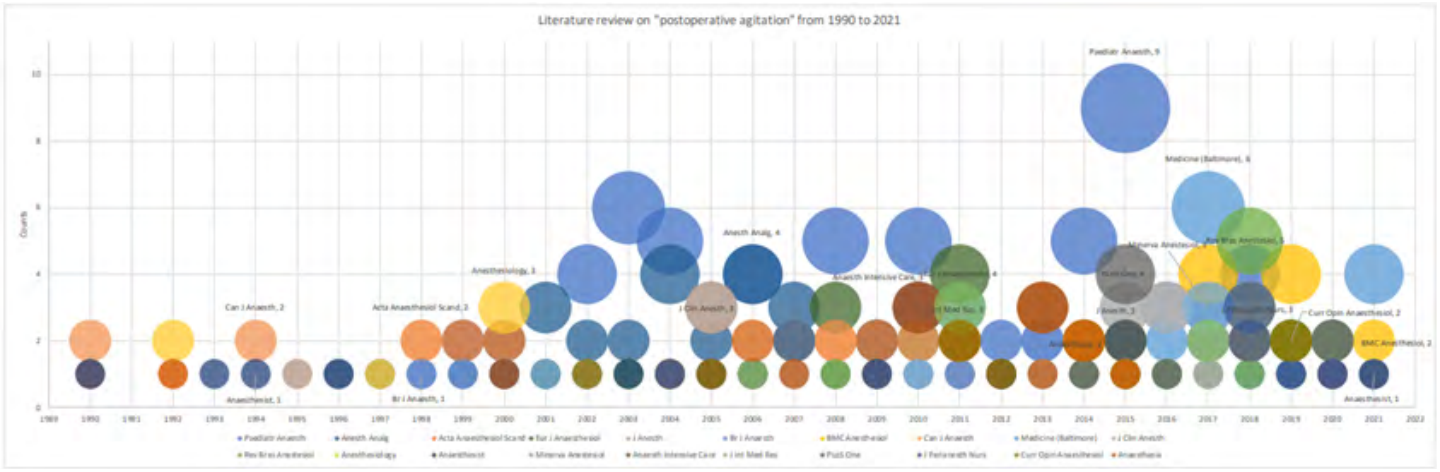

Figure 2: Bubble plot of literature analysis from 1990 to 2021. Journals publishing more than 10 articles in the field of postoperative agitation were all listed.

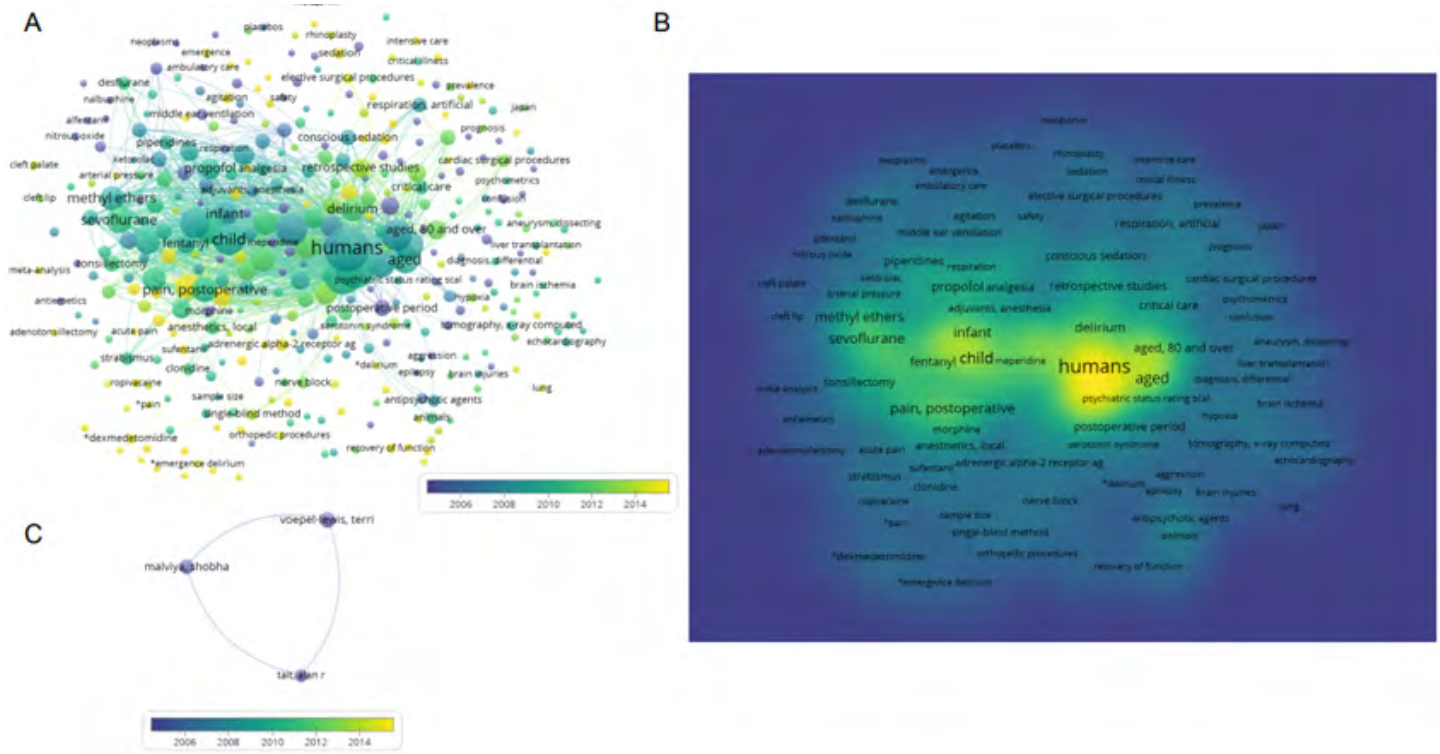

Figure 3: Bibliometric analysis of all keywords in publications of postoperative agitation. (A) co-occurrence analysis of overall keywords; the size of nodes indicates the frequency of occurrence. The curves between nodes represent their co- occurrence in the same publication. (B) Item density plot of keywords. Each point in the item density visualization has a color that indicates the density of the item at that point. Colors range from blue to green to yellow. The more the numbers of items near a point is, the higher the weight of adjacent item is, and the color of the point is closer to yellow. (C) The co-authorship map of authors which indicates the authors that cooperate in the field of postoperative agitation.

5. Conclusion

Postoperative agitation is a common and significant problem which may affect the safety of patients and medical care team. Research concerned about this topic in adults is relatively rare. Definition, diagnosis, mechanisms, risk factors, prevention strategy and management are all need to be further clarified. In this case report and literature review, we reported a case with unique risk factor and treatment measure, summarized related clinical studies and analyzed the trend and current research status on this subject for further exploration.

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