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Influence of various techniques of preemptive analgesia on perioperative outcomes in patients undergoing vitrectomy – review

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Abstract

Vitrectomy is one of the most widely performed precise procedures in ophthalmic surgery. Although usually carried out under local anaesthesia, in selected cases general anaesthesia is the only possible alternative to carry out procedure safely and ensure optimal analgesia. Bearing in mind the burden of all negative effects of opioid analgesics administered systemically during general anaesthesia, the concept of preemptive analgesia was developed to reduce intraoperative opioid requirements and diminish their adverse effects. Applying analgesic treatment prior to surgical incision enables maintaining stable intra- and postoperative analgesia and thus results in opioid sparring and improves perioperative outcomes by reducing adverse event rates (such as postoperative nausea and vomiting, occurrence of ocluocardiac reflex, postoperative intolerable pain perception) during vitreoretinal surgery. In this study, several methods of preemptive analgesia and their influence on perioperative outcomes in patients undergoing vitrectomy will be discussed. *Anestezjologia i Ratownictwo 2022; 16: 208-214. doi: 10.53139/AIR.20221623*

Keywords: vitrectomy, preemptive analgesia, postoperative nausea and vomiting (PONV), oculo-cardiac reflex (OCR), postoperative pain

Introduction

Vitrectomy (*vitreoretinal surgery, VRS* or *pars plana vitrectomy, PPV*) is one of the most widely performed precise procedures in ophthalmic surgery, that includes removing vitreous humour from eye with the use of microscope and microtools.

First performed in 1968 by David Kasner, using open eye technique, its present form, in closed system, was developed by Robert Machamer, widely acknowledged as a father of vitreoretinal surgery [1]. Machamer in 1970 developing his proprietary set of tools (including *Vitreous Infusion Suction Cutter, VISC*), marked a milestone for VRS (and the beginning of what became finally known as pars plana vitrectomy), as it allowed a controlled access to posterior part of an eyeball [2]. Nowadays PPV is carried out in three - port vitrectomy system, with dedicated ports for microtools, infusion of fluid to maintain IOP, and illumination of the posterior segment. The development of abovementioned technique allowed it to became an almost routine procedure, which can be performed, with outstanding outcomes, by an experienced operator in outpatient system.

Indications for PPV include various problems affecting posterior part of the eye and can be divided into diagnostic (controlled biopsy in order to obtain biological material for further microbiological, biochemic, histopathological and genetic analyses) [3,4] and therapeutical in case of vitreoretinal haemorrhage, tractional retinal detachment, idiopathic macular hole, epiretinal membrane, diabetic macular edema, eye trauma or suspicion of intraocular foreign body [3].

As every surgical procedure, PPV has its contradic-

tions, which in case of urgent indications (such as endophthalmitis, vitreoretinal haemorrhage or eye trauma) can be omitted in order to save patient's eyesight or the eyeball as a whole. In such case the only contradiction is patient's general condition or the inability of restoring eyesight despite performed surgery. In elective PPV the biggest concern, and indication to cancel or postpone procedure, is patient's use of medications that alter blood coagulation [2]. But, as found in literature, in most cases when there is increased risk of thromboembolic complications it is not recommended to stop antiplatelets drugs or warfarin [5] and the gravity of decision to perform a surgery despite this relative contraindication rests with the operator.

Another challenge to face during PPV is choosing anaesthetic approach which is crucial in providing appropriate care in the perioperative period. The main goal is to ensure patient's safety and facilitate the procedure while simultaneously block any noxious stimuli that can lead to unpleasant adverse events like postoperative intolerable pain perception (*PIPP*). Inappropriate nociception - antinociception balance during PPV can result in grave complications such as hemodynamical instability and occurrence of ocluocardiac reflex (*OCR*) – both being an enormous threat, yet potentially possible to prevent with adequate analgesia. Several approaches are possible to provide anaesthesia for patients undergoing PPV. Development of ophthalmic microsurgery has led to shortening the duration of performed procedures and thus allowed to carry out most of them under local anaesthesia (*LA*): peribulbar (*PBB*) and retrobulbar block (*RBB*) or topical anaesthesia (*TA*) [6]. The benefit of such proceeding includes its minimal interference with homeostasis (lower risk of respiratory or cardiac failure, nausea and vomiting). What is more, longer duration of analgesic effect of LA in postoperative period adds to its advantage. But at the same time one cannot forget that inability to immobilize patient's head during surgery performed under LA or TA in combination with insufficient sedation can gravely compromise procedure's safety. Therefore, in large group of patients, especially in elderly, with elevated perioperative stress level, cognitive decline and diseases or with spinal arthritis that prevents maintaining horizontal position over a long period of time, general anaesthesia (*GA*) is the only possible alternative to carry out PPV safely and ensure optimal analgesia. However, classical opioid – based GA carries the burden of all negative effects of opioid analgesics (*OA*) administered systemically (such as elevated risk of postoperative nausea and vomiting (*PONV*), hyperalgesia). The concept of opioid – free anaesthesia (*OFA*) was developed to reduce intraoperative opioid requirements (and diminish the adverse effects of OA) by blocking afferent noxious impulses with LA, TA or intravenous analgesics, while maintaining immobilization with GA [7], whereas preemptive analgesia (*PA*) refers to the administration of an abovementioned analgesic treatment prior to surgical incision to prevent central sensitization [8].

The aim of this review was to assess the influence of various techniques of preemptive analgesia on perioperative outcomes (such as PONV, OCR, and PIPP) in patients undergoing vitrectomy.

Preemptive Analgesia (PA)

Preemptive analgesia is a technique that refers to the administration of analgesics prior to surgical incision (in contrast to preventive analgesia where intervention can be performed either intraoperatively or postoperatively) [8]. There are several methods of PA than can be applied in ophthalmic surgery of which selected examples are described below.

Local anaesthesia is widely recognised PA method to ensure stable intra- and postoperative analgesia in eye surgeries. Peribulbar block (PBB) is the administration of local anaesthetic outside the orbital muscle cone, while retrobulbar block (RBB) is the administration of anaesthetic more posteriorly into the retrobulbar space within the muscle cone [9]. The addition of one of the abovementioned blocks to the GA, according to numerous studies in the literature [10-15] provides adequate analgesia throughout the surgery.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as metamizole and acetaminophen are an efficient alternative to LA because of their widely recognised good analgesic effect and relatively low risk of adverse events [16,17]. Both acetaminophen and metamizole's metabolites main mechanism of action is the inhibition of the enzyme cyclooxygenase (COX) – acetaminophen: COX-2 and COX-3, metamizole: COX-1 and COX-2 [8,18,19]. Moreover, acetaminophen influences serotonergic antinociceptive system (through 5-HT1A receptors) [16,17,19] and stimulates endocannabinoid system (CB1 receptors) [17,19]. Whereas metamizole omni-directional action, apart from influencing prostaglandins synthesis routes, includes inhibiting

substance P-induced nociception and influencing endocannabinoid system [17,20]. In connection with the above, acetaminophen and metamizole characterize high effectiveness both in postoperative pain treatment and as an element of preemptive analgesia technique.

Topical anaesthesia is the administration of anaesthetic drops onto the ocular surface [21]. It is relatively safe, easy to administer and widely accepted by patients method to obtain rapid analgesia [22]. Even though most often applied in cataract surgery [9,22], as showed in various studies in the literature [23,24], allows to maintain adequate analgesia during VRS and plays significant role in PA.

Postoperative Nausea and Vomiting (PONV)

PONV is defined as every nausea, gag reflex and vomiting experienced by a patient within 24 – 48 hours following surgical procedure, with prevalence rate 30% - 80% in high risk groups [25,26].

The Apfel Score for Postoperative Nausea and Vomiting predicts risk of PONV in adults [26,27]. It is an easy tool to recognise the high risk patients using 4 independent risk factors (female sex, non-smoking status, history of PONV or motion sickness, postoperative opioid use) and enables anaesthesia providers to match antiemetic strategies with the calculated score. Patients with 0 – 1, 2 or 3 risk factors are respectively allocated to low, moderate or high risk category [27].

On the other hand, in the study performed by our faculty we analysed independent risk factors for PONV occurrence (such as gender, Body Mass Index, arterial hypertension, diabetes mellitus, history of motion sickness, smoking status or intraoperative opioids consumption) in patients undergoing PPV under general anaesthesia. Yet, surprisingly, with the exclusion of diabetes, the results were not statistically significant – none of the abovementioned factors elevated the risk of PONV [28].

In current literature the prevalence of PONV during intraocular procedures is estimated between 18% and 56% [29]. Meanwhile, PONV is reported in 15 – 60% patients undergoing PPV [30,31].

It is a challenge both for anaesthesiologist and surgeon, as PONV is reported to be one of the most common reasons for lack of patient's satisfaction from performed procedure and is associated with grave complications such as dehydration, pulmonary aspiration, wound dehiscence and in consequence prolonged hospitalization and rise in total cost of care [26,32]. Every PONV episode in patients undergoing PPV may result in abrupt raise of intraocular pressure (*IOP*) and undermine the success of performed procedure as well as is a known risk factor of occurrence of intraocular haemorrhage [33].

It is widely known fact that OA are responsible of dose – related influence on higher risk of occurrence of postoperative nausea and vomiting by delaying gastric emptying [25,26]. Mandelcorn et al. [34] in their work observed the occurrence of PONV three times more often in patients undergoing PPV under conscious sedation when additional intraoperative use of opioid analgesics was necessary. Therefore, the intraoperative use of OA was mean risk factor for nausea in the first 24 hours after vitrectomy.

Opioid sparing during GA can be potentially obtained by using one of the abovementioned techniques of preemptive analgesia: local anaesthesia or intravenous analgesics.

Carvalho et al. [35] reported statistically lower incidence of PONV in group of patients that underwent PPV under local anaesthesia (*PBB*) in comparison to general anaesthesia. Abouammoh et al. [36] made similar conclusions: they compared GA with GA in combination with LA (preemptive sub-Tenon's anaesthesia) – the prevalence of PONV was lower (14% vs 5%) in group with additional LA. Also Ghali et al. [10] and Mahfouz et al. [15] reported that additional LA with GA resulted in less frequent PONV episodes than classical GA (respectively 10% vs 33% and 2% vs 9%). Moreover Heinke et al. [37] in their study observed that total intravenous anaesthesia (*TIVA*) with propofol and alfentanil correlated with lower incidence of PONV than balanced GA (16% vs 43.5%) with additional drop to 4.7% when antiemetic prophylaxis was administered.

Intravenous analgesics such as metamizole and acetaminophen are popular non-opioid analgesic drugs. Both being widely available and relatively safe are good alternative to LA in terms of preemptive analgesia. Moreover, it is extensively described in literature that acetaminophen due to its complimentary antiemetic properties potentially decreases the risk of PONV [38,39]. Brodner et al. [40] confirmed in their study that acetaminophen, when administered preoperatively before induction of GA, reduces number of episodes of PONV. Sadrolsadat et al. [41] in their

double-blind clinical trial proved that preoperative administration od acetaminophen lowers the incidence of PONV in comparison to control group with saline infusion, although the difference was statistically insignificant. On the other hand, study carried out by Landwehr et al. [42] did not prove this hypothesis – preemptive analgesia using metamizole or acetaminophen was proven to be unsuccessful in lowering the risk of PONV despite its opioid sparing effect in comparison to the control group with GA only.

Oculocardiac Reflex (OCR)

The occurrence of oculocardiac reflex (*OCR, trigeminocardiac reflex*) is very serious intraoperative challenge, both for the operator and anaesthesiologist. OCR is defined as a sudden decrease in heart rate by greater than 20% [43]. As stated in literature, the incidence of OCR is reported between 16% to 85% of all procedures performed on face and neck area as a result of mechanical stimulation of trigeminal nerve [43, 44]. The reflex most commonly results in sinus bradycardia, but can also manifest as a drop in arterial pressure, various arrhythmias, and, in extreme cases even cardiac arrest [44]. Therefore, OCR is circulatory system's response to inadequate intraoperative analgesia expressed as cardiac arrythmia in reaction to direct pressure placed on the extraocular muscles, globe or conjunctiva. Adequate GA with preemptive analgesia blunts OCR, thus ensures hemodynamical stability and with opioid sparing effect allows to avoid OA's adverse effects.

It is extensively described in literature that addition of local anaesthesia to GA reduces the incidence od OCR. Rahimi et al. [44] proved that applying tetracaine eye drop as a topical nerve blocker lowers the risk of OCR during the incision stage of strabismus surgery. Ghali et al. [10] observed OCR in 8 out of 30 patients (27%) that underwent PPV under GA, and in 2 out of 30 patients (7%) when there was an additional PBB performed. Shende et al. [45] in their study compared patients undergoing elective PPV following retinal detachment under GA vs GA with preemptive LA (PBB+GA) – OCR was observed in 70% of patients in GA group and 30% in PBB+GA group. Abdeldayem et al. [46] proved that addition of sub-Tenon's block to GA reduces incidence of OCR: - 7.5% vs 15% in control group. Similar results were shown in study performed by Abouammoh et al. [36] – additional sub-Tenon's block reduces incidence of OCR from 16% to 5% (control vs sub-Tenon's block group).

By this time, based on the current literature, there are no studies available that investigate the influence of preemptive analgesia with intravenous analgesics (metamizole, acetaminophen) on the incidence of OCR during vitrectomy.

In contrast, study performed by our faculty [47] showed no statistically significant differences in OCR occurrence between groups with additional preemptive analgesia (local anaesthesia or intravenous analgesics) vs control group (GA only). The crucial difference between abovementioned studies and our study was that we administered OA strictly under Surgical Pleth Index (*SPI*) that was not used in mentioned studies. Therefore, the key to reduction in OCR incidence was stable analgesia under Adequacy of Aneasthesia (*AoA*) guidance, not necessarily the addition of PA, as stated in the literature.

Postoperative Intolerable Pain Perception (PIPP)

Pain is very complex phenomenon, both on physiological and behavioural level. Moreover, clinical assessment of postoperative pain is a great challenge for both physician and their patient. One of the most used tools to determine the level of postoperative pain experienced by the patient is Numerical Rating Scale (*NRS*). NRS consists of 11 points where 0 is no pain and 10 is the worst pain imaginable. The pain scores are interpreted as:
0 = no pain
1–3 = mild pain
4–6 = moderate pain
7–10 = severe pain [48].

Vitrectomy, although associated with meagre tissue damage, can lead to acute postoperative pain. PIPP is defined as pain measured in NRS > 3.

Fekrat et al. [49] investigated levels of eye pain, following vitreoretinal surgery – 56% of patients reported pain postoperatively, moreover, 48% of patients received an analgesic agent within 5 hours after surgery, and in 27% of cases an opioid analgesic was required.

In study presented by Schönfeld et al. [11] GA with additional PBB proved to be an efficient way to prevent PIPP (60% of patients reported no pain one hour after the surgery). Once again Ghali et al. [10] proved the superiority of GA with PBB in comparison to GA – 7%

of patient in group with combined anaesthesia reported PIPP vs 30% of patients where only GA was administered. Moreover, patients in control group required higher doses of tramadol and diclofenac postoperatively than in PBB group. On the other hand, in study by Bayerl et al. [13] PBB performed preoperatively (prior to induction of GA) was not beneficial in OA sparing during the surgery and had no influence on pain scores observed postoperatively. However, patients in control group were given non-steroidal anti-inflammatory drugs (*NSAIDs*) on emergence from GA, what was a serious deranging factor.

In the literature, there are many studies investigating beneficial influence of lowering incidence of PIPP by administering cyclooxygenase inhibitors as a preemptive analgesia. De Araújo et al. [50] showed that infusion of 1 g of metamizole 40 minutes before induction of GA significantly reduced pain scores in patients undergoing PPV in comparison to placebo group. Similar effect of administering 1 g of metamizole or acetaminophen as PA was described by Landwehr et al. [42] – both drugs were proven as an efficacious method of assuring stable postoperative analgesia in comparison to control group, where PA was omitted. Likewise, Sadrolsadat et al. [41] investigated analgesic potential of acetaminophen administered either prior to induction of GA (preemptive analgesia) or on emergence from GA (preventive analgesia) – in both groups pain scores (and the incidence of PIPP) were lower in comparison to control group. On the other hand, Vaideanu et al. [51] did not observe any statistically significant effect of acetaminophen on reducing PIPP – in both group pain scores were comparable. However, in comparison to placebo group, none of the patients in the acetaminophen group reported increased total pain at 24 hours (vs 6 patients in placebo group).

Recalling yet again our own study, 33 patients despite of a group allocation reported NRS level > 3 after VRS (most from the metamizole and topical anaesthesia groups), however statistical analysis showed no statistical significance, what proved no superiority in means of the type of PA used in comparison to control group [52].

Conclusions

Currently the concept of preemptive analgesia is widely recognised as an efficient way of maintaining safe and stable analgesia both intra- and postoperatively. Moreover, in the light of various studies confirming opioid's numerous side effects, especially with impact on delivery of enhanced recovery and on a patient's postoperative outcomes, PA role in ERAS (*Enhanced Recovery After Surgery*) protocol cannot be overestimated [53]. The PA methods described above are capable of not only aiding in sparing OA resulting in, among others, lowering the risk of PONV, but also ensuring adequate analgesia, and thus preventing the occurrence of potentially either perilous or burdensome adverse event such as OCR and PIPP. However, it must be stressed that every patient's case needs to be assessed individually, as the administration of regional or intravenous analgesia carries the burden of rare potential perioperative complications and can outweigh its potential benefits.

Conflict of interest
None

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