Research Article

Evaluation of the Effect of Neostigmine as Adjuvant to Local Anesthetic Mixture in Peribulbar Anesthesia

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Abstract
Objective: To assess the effect of adding neostigmine ٠.٥ mg as adjuvant to local anesthetic mixture in peribulbar anesthesia. **Methods:** Sixty six patients ASA physical status I or II scheduled for trabeculectomy under peribulbar anesthesia were randomly divided into two equal groups. Group N (n=٣٣) received local anesthetic mixture plus ٠.٥ mg neostigmine while group C (n=٣٣) received local anesthetic mixture alone. Onset, duration of globe anesthesia, globe akinesia, lid akinesia, time for adequate conditions to start surgery, time to ١st analgesic request, patient satisfaction, surgeon satisfaction, and any complications due to the used drugs were examined and recorded. **Results:** Onset of globe anesthesia, lid akinesia, and globe akinesia was more rapid in neostigmine group than the control group, and this difference was statistically significant. There was a significant prolongation of the duration of sensory, motor block, and time to ١st analgesic request. **Conclusion:** This study concluded that addition of ٠.٥ mg neostigmine to local anesthetic solution in peri bulbar anesthesia accelerated the onset of sensory, motor block, time for adequate conditions to start surgery, prolonged the duration of sensory and motor block, delayed the time of ١st analgesic request, increased satisfaction of the patients, and improved quality of surgical conditions without any side effects.
Keywords: Neostigmine, trabeculectomy, Peribulbar anesthesia

Introduction
Regional anesthesia is the preferred type of anesthesia for eye surgeries because it has many advantages as it is more safe in elderly patients who are candidates for ophthalmic surgeries and they usually have multiple systemic diseases making them more liable for anesthetic complications[١].

Additional advantages of regional anesthesia is its ability to prevent endocrinal and metabolic response associated with the surgery, it is more suitable for day case surgery, and it is associated with less incidence of nausea and vomiting[٢].

Increased incidence of complications associated with retrobulbar anesthesia such as brainstem anesthesia, globe perforation, and retrobulbar hemorrhage made the peribulbar anesthesia is more preferred in ophthalmic operations, but it is not free from disadvantages such as its slow onset, its short duration, and its need to high volume of local anesthetic which may increase the intraocular pressure (IOP)[٣]. Many additives were added to the local anesthetic in peribulbar anesthesia to overcome these disadvantages such as hyaluronidase[٤], clonidine[٥], and muscle relaxants[٦].

Trabeculectomy is the most commonly used surgery for lowering intraocular pressure by providing ap assage to the subconjunctival space and it requires deep anesthesia which needs large volume of local anesthetic with subsequent rise in the IOP making more difficulty to the surgeon[٧].

Neostigmine is a parasympathomimetic drug which binds to the active side of acetylecholine estrase enzyme preventing it from hydrolysis of the acetylecholine

molecules leading to increased level of acetylecholine at peripheral muscarinic receptors present in the peripheral nerve ending[٨] leading to activation of cholinergic-mediated antinociception by activation of No-cGMP pathway and this in turn leads to prolongation of post operative analgesia[٩].

Many researches examined the analgesic effects of peripherally administered neostigmine as in intravenous regional anesthesia[١٠], intraticular[١١], and in axillary block[١٢]. They reported that addition of neostigmine to the local anesthetic solution accelerated the onset of anesthesia, prolonged its duration, and prolonged time to ١st analgesic request.

It was hypothesized that adding neostigmine to the local anesthetic mixture in peribulbar anesthesia for trabeculectomy surgery would improve quality of anesthesia and analgesia produced by peribulbar anesthesia.

The aim of this randomized double blinded study was to evaluate the effect of adding ٠.٥mg neostigmine to local anesthetic mixture in peribulbar anesthesia on onset of sensory and motor block (primary outcome), duration of sensory and motor block, need for block supplementation, volume of local anesthetic used, time of ١st analgesic request, satisfaction of the patients, quality of operative conditions and side effects of neostigmine as bradycardia, diarrhea, nausea, vomiting and abdominal cramps (secondary outcomes).

Methods

This prospective, randomized, double blinded study was performed in El –Minia university hospital in the period from January ٢٠١٣ to November ٢٠١٣. After obtaining approval of the ethics committee of faculty of medicine in El-Minia university and informed written consents from the patients and after a pilot study on five patients, and their follow up for one month by the ophthalmologist till complete healing, recovery, and getting sure that there was no side effects related to the drug on the surgery. Sixty six patients ASA physical status I or II aged from ٥٠ to ٧٠ years scheduled for trabeculectomy operation under peribulbar anesthesia were included in the study. Patients with coagulopathy or on anticoagulant therapy, infection in the site of the block, axial length more than ٢٦ mm or posterior staphyloma, allergy to LA used, uncooperative patients (mental retardation, deafness), body mass index >٣٥, patients with bronchial asthma, patients with brady arrhythmias and those who refused to participate in the study were excluded from the study.

Patients were allocated randomly into two equal groups each of which was thirty three patients using computer generated randomized numbers, the allocation ratio was ١:١ and the identification cards were put in a sealed opaque envelops to hide the allocation. They were divided according to the used local anesthetic solution into two groups:

- Group N (n=٣٣): they received ٣ ml of isobaric bupivacaine ٠.٥٪ plus ٣ ml of lidocaine hydrochloride ٢٪ containing ٩٠ IU of hyaluronidase plus ١ ml (٠.٥mg) of neostigmine so the anesthetic solution was seven ml volume in ten ml syringe.
- Group C (n=٣٣): they received ٣ ml of isobaric bupivacaine ٠.٥٪ plus ٣ ml of lidocaine hydrochloride ٢٪ containing ٩٠ IU of hyaluronidase (hyaluronidase ١٥٠٠ IU powder dissolved in ٥٠ cc bottle of lidocaine hydrochloride so each ١ ml of lidocaine contained ٣٠ IU hyaluronidase) plus ١ ml normal saline so the anesthetic solution was seven ml volume in ten ml syringe.

Local anesthetic solution was prepared by anesthesiologist not included in the study in syringes of equal volume for the purpose of blindness so neither the patients nor the anesthesiologist knew the components of the solution. All patients were fasted for ٦ h pre-operatively, and they received ١٥٠ mg oral ranitidine on the morning of the surgery. At the operation room ٢٢gauge cannula was inserted in dorsum of non

dominant hand and the patients were attached to a multi-channel monitor (Hewlett Packward, Viridia ٢٤ Germany) to record base line Electrocardiogram (ECG), heart rate (beats /min), systolic, diastolic blood pressure, and oxygen saturation ($SpO_٢$). Patients lied in supine position with nasal cannula which delivered oxygen at ٣ L/minute.

Anesthetic technique: The injections will be carried out using a (٢٥G) needle with a length of ٢٥mm being connected to the syringe contained the anesthetic solution. The patients lied supine and look directly ahead focusing on a fixed point on the ceiling, so that the eyes were in the neutral position. After sterilization of the lower eye lid, the globe was pushed up by the nondominant hand of the anesthetist while the needle was introduced at a point ١-١.٥ cm medial to the lateral canthus, on the inferior eyelid and directed slightly medially (٢٠^{o}) and cephalad (١٠^{o}) until needle hub contact the skin. After negative aspiration, the local anesthetic mixture according to patient's group was injected guarded by no overcrowding of the eye. Time to complete the injection was considered as ٠ time, then soft intermittent digital pressure by the middle three fingers on the eye was applied for ٥ minutes to decrease the intraocular pressure, help spread of the anesthetic solution and promote akinesia of periorbital muscles.

The following parameters were recorded:

- Hemodynamic parameters such as heart rate (beats/min), and non invasive blood pressure (mmHg) and oxygen saturation were recorded just before peribulbar injection (base line), and every five minutes till the end of surgery.
- Onset of sensory block in minutes which was calculated from the time of injection till complete loss of corneal sensation which was assessed by gentle touching of the cornea with a cotton swab. Duration of sensory block was calculated till the beginning of sensation.
- Onset and duration of motor blockade of the eye globe (globe akinesia) which was assessed using three point scale[١٣] ranged from ٠-٢ in each direction. Akinesia score is equal to the sum of the scores in the four directions ranging from ٠ to ٨. It was performed by asking the patient to look superior, inferior, medial and lateral every minute till ١٠ minutes. Onset of globe akinesia was calculated from the time of complete injection of the local anesthetic till the complete akinesia (akinesia score ٠) while the duration was calculated from the injection time till complete recovery of motor power (akinesia score ٨).
- Onset and duration of lid akinesia was assessed by testing the ability of the patient to open (levator muscles), and to close (orbicularis muscle) the eye. Where ٠= Complete akinesia, ١=Partial move-ment in either or both eyelid margins, ٢= Normal movement in either or both eyelid margins [١٣]. Onset of lid akinesia was calculated from the time of complete injection of the local anesthetic till the occurrence of complete lid akinesia. Duration of the lid akinesia was calculated from injecting the anesthetic solution till complete recovery from the block occurred. A second dose (٣ ml) of the local anesthetic solution may be needed if the block is incomplete after ١٠min from the first injection if there was incomplete block as manifested by the full movement in any direction or ocular akinesia score $\geq$ ٦ could be given as an augmentation to the first injection between the caruncle and the medial canthus, passing back with the bevel facing the globe. Number of patients needed second injections was recorded in each group.
- Total volume of local anesthetic solution used to obtain adequate akinesia.
- Time for adequate conditions to start the operation (corneal anesthesia plus globe akinesia score $\leq$ ١ and eyelid akinesia score of ٠).
- Duration of surgery.

- Quality of operative condition assessed by the surgeon at the end of the surgery and it was as follow: ٠ = unsuccessful (Failed to work), ١ = poor (Inadequate for surgery) ٢ = acceptable (Block is incomplete but surgery could proceed) ٣ = perfect (Effective block).
- Patient satisfaction score: It was assessed by asking the patient at the end of the surgery, it was as follow: ١= Complete dissatisfaction, ٢= some dissatisfaction, ٣= Complete satisfaction.
- The time to ١st analgesic request (calculated from the time of complete injection of the local anesthetic till visual analogue scale was ≥٣) was recorded. The patients received intravenous ketrolac ٣٠ mg on request.
- Complications either related to neostigmine as (bradycardia, bronchospasm, increased salivation, nausea, vomiting, diarrhea, and colic) or related to the technique (brain stem anesthesia, retrobulbar hemorrhage, globe perforation).

At the end of the surgery, patients were transported to the post anesthesia care unit (PACU) till stable vital signs, and absence of nausea and vomiting or any side effects, then they were transported to the ward.

Statistical analysis

Using PASS (Power Analysis and Sample Size System) software (NCSS, East Kaysville, Utah, USA), it was found that the least number of patients required in each group to detect ٢ minutes difference in the onset of ocular akinesia with ٩٥٪ power and ٠.٠٥٪ significance level was ٣٠ patients and with ١٠٪ dropout ratio, the number was increased to ٣٣ patients in each group.

Data were analyzed with Statistical Program SPSS version ٢١ (SPSS Inc., Chicago, IL, USA). Numerical results were expressed as mean ± SD, while categorical results were expressed as number and percentage. Results were tested for normal distribution by Kolmogorov-Smirnov test. Student's T test was used to compare the numerical data between the two groups. Categorical results were analyzed by Fisher's exact test. All tests are two-tailed and *P* value of <٠.٠٥ was considered significant.

Results

Seventy patients were examined for eligibility of the study, four of them refused to participate in the study and sixty six patients participated and completed the study to analysis of the results figure (١).

There was no significant difference between the two groups as regards the demographic data, duration of the surgery, or the axial length of the eye table (١). As regards time of onset of lid akinesia, globe akinesia, sensory block, and time for suitable conditions to start surgery, they were more rapid in the neostigmine group than the control group and this difference was statistically significant table (٢). As regards the duration of lid akinesia, globe akinesia, sensory block, and time to ١st analgesic request, they were significantly prolonged in the neostigmine group than the control group table (٣).

The total volume of local anesthetic used and the need for ٢nd injection was less in the neostigmine group than the control group table (٤). More patients in neostigmine group were satisfied about anesthesia and pain management than the control group table where ٢٦ patients were completely satisfied in neostigmine group while only ١٧ patients were completely satisfied in control group table (٥). As regards the quality of surgical block which was assessed by the surgeon, it was perfect in more patients in the neostigmine group than the control group table (٦). There were no side effects related to neostigmine use as bradycardia, abdominal colic, increased salivation, or bronchospasm.

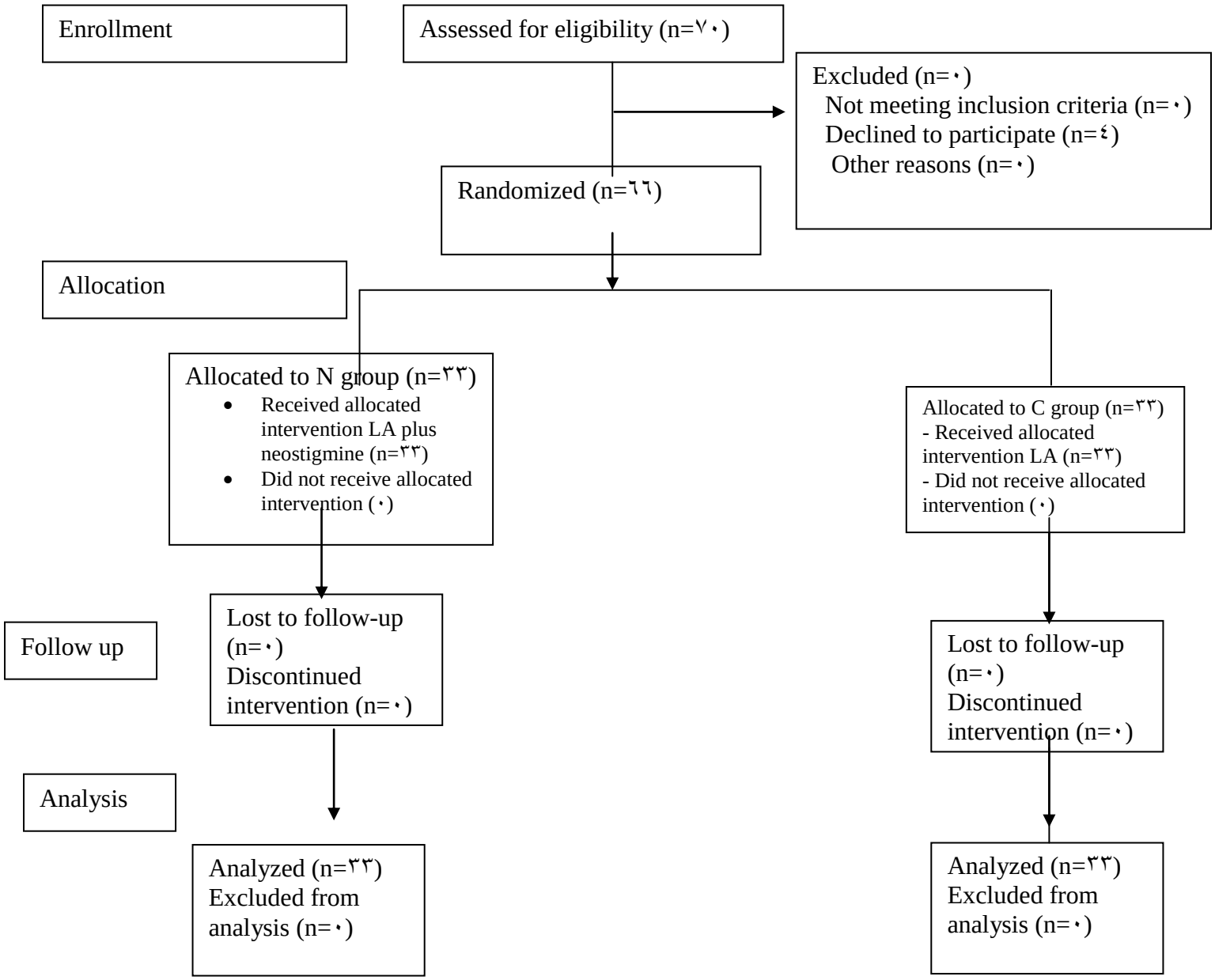

Figure (١): Flow chart in the study.

Table (١): Characters of the patients and duration of the surgery

item	Group N (n=٣٣)	Group C (n=٣٣)	*P* value
Age in years	٥٨ ±٧.١	٥٧.٢ ± ٤.٢	٠.٥٧٩
sex♂/♀	١٣/٢٠	١١/٢٢	٠.٦٠٩
Weight (kg)	٧٤.٧ ± ٦.٤	٧٣.٢ ± ٥.٧	٠.٣١٨
Axial length(mm)	٢٤.٠ ±١.٢	٢٣.٨ ±١.٦	٠.٥٦٨
Duration of surgery (minutes)	٣٠.٧ ± ٥.٤	٣١ ± ٦.١	٠.٨٣٣

Data are expressed as mean ± SD. Sex is expressed as numbers.

Table (٢): Onset of lid akinesia, globe akinesia, sensory block, and time for suitable conditions to start surgery.

Item	Group N (n=٣٣)	Group C (n=٣٣)	*P* value
Onset of lid akinesia (minutes).	٣.٥ ± ٠.٧*	٤.٥ ± ٠.٨	<٠.٠٠١*
Onset of globe akinesia (minutes).	٤.٨ ± ١.٣*	٥.٩ ± ١.١	<٠.٠٠١*
Onset of sensory block (minutes).	١.٩ ± ٠.٤*	٢.٦ ± ٠.٥	<٠.٠٠١*
Time for suitable conditions to start surgery (minutes).	٦.٧ ± ١.٣*	٨.٨ ± ٢.١	<٠.٠٠١*

Results are expressed as mean ± SD. *P* value < ٠.٠٥ considered significant.

Table (٣): Duration of lid akinesia, globe akinesia, sensory block and Time to ١st analgesic request.

Item	Group N (n=٣٣)	Group C (n=٣٣)	*P* value
Duration of lid akinesia (minutes).	١٣٨ ± ١٤.٢*	١٠٨ ±٧.١	<٠.٠٠١*
Duration of globe akinesia (minutes).	١٨٤ ± ١٧.١*	١٤١ ± ٦.٤	<٠.٠٠١*
Duration of sensory block (minutes).	٦٨.٢ ± ٤.٦*	٥٩.٧ ± ٤.٧٢	<٠.٠٠١*
Time to ١st analgesic request (minutes)	٢٠٦.٤ ± ١٤.٢*	١٥٤.٣ ± ١١.٤	<٠.٠٠١*

Results are expressed as mean ± SD. *P* value < ٠.٠٥ considered significant.

Table (٤): Volume of LA used and incidence of ٢nd injection.

Item	Group N (n=٣٣)	Group C (n=٣٣)	*P* value
Volume of LA used (ml)	٧.٥ ± ١.٢	٨.١ ± ١.١	٠.٠٣٨*
Need for ٢nd injection	١٥ (٤٥.٤٪)	١٠ (٣٠.٣٪)	٠.٢٠٥

Results are expressed as mean ± SD. *P* value < ٠.٠٥ considered significant.

Table (٥): Satisfaction of the patients in the two groups.

Patient Satisfaction Score	Group N (n=٣٣) N (%)	Group C (n=٣٣) N (%)	P value
Dissatisfaction	٠ (٠٪)	٤ (١٢.١٪)	٠.٠٣٩*
Some dissatisfaction	٧ (٢١.٣٪)	١٢ (٣٦.٤٪)	٠.١٧٤
Complete satisfaction	٢٦ (٧٨.٧٪)	١٧ (٥١.٥٪)	٠.٠٢٠*

Results are expressed as number of patients and percentage. *P* value < ٠.٠٥ considered significant.

Table (٦): Quality of the block in the two groups.

Quality of block	Group N (n=٣٣) N (%)	Group C (n=٣٣) N (%)	P value
Acceptable	٩ (٢٧.٣٪)	١٨ (٥٤.٥٪)*	٠.٠٢٤
Perfect	٢٤ (٧٢.٧ %)*	١٥ (٤٥.٥٪)	٠.٠٢٤

Results are expressed as number of patients and percentage. *P* value < ٠.٠٥ considered significant.

Discussion

This study found that adding ٠.٥mg of neostigmine to the local anesthetic solution in peribulbar anesthesia for trabeculectomy accelerated the onset time of sensory and motor block, accelerated time for suitable conditions to start surgery, prolonged the duration of the block, and delayed the time to ١st analgesic request without any side effects.

The dose of ٠.٥ mg neostigmine was chosen based on previous study by Lauretti et al.,[١١] on ٥٨ patients scheduled for knee surgery to identify the possible site of analgesic action of neostigmine. They compared between postoperative analgesic effect of ١ µg/kg epidural neostigmine, ١µg/kg intra-articular neostigmine, and finally ٥٠٠ µg/kg intra-articular neostigmine and they found that to obtain the same post-operative analgesic effect, the peripheral dose should be five folds of the central dose of neostigmine. Yang et al.,[١٤] who found that the peripheral effective dose of neostigmine for postoperative analgesia was ten folds of the intrathecal dose which was ٥٠ µg neostigmine, and the study of Sethi and Wason[١٥] who used ٠.٥ mg neostigmine as additive to ٤٠ ml of ٠.٥٪ lidocaine in the intravenous regional anesthesia in upper limb surgery and they found that neostigmine shortened the onset time of sensory and motor block and prolonged the post operative analgesia without any side effects.

This study chose the operation of Trabeculectomy because it doesn't need mydriasis which may be conflicted by neostigmine, although no myosis was noticed in any patient during the study.

The results of the current study coincides with the results of Honarmand et al.,[١٦] in their double blinded study on ٨٠ patients undergoing knee arthroscopy in which they evaluated the effect of adding two dose of neostigmine to intrathecal hyperbaric bupivacaine ٠.٥٪ and they concluded that intrathecal neostigmine enhanced spinal anesthesia and prolonged postoperative analgesia for ٢٤ hours with no side effects.

Lauretti et al.,[١٧] in their double blinded study on ٤٨ women undergoing vagino-platsy to compare between the effect of adding different doses of intrathecal neostigmine (٥٠,١٠٠,٢٠٠µg) in subara-chnoid anesthesia and intrathecal morphine, and they found that intrathecal neostigmine produced postoperative analgesia similar to intrathecal morphine in the duration with less side effects.

As regards the duration of motor block, the current study found that neostigmine prolonged the duration of globe and lid akinesia, this was in agree with Tan et al.,[١٨] who compared the analgesic efficacy and safety of intrathecal neosti-gmine (٥٠µg) and intrathecal morphine (٣٠٠ µg) in their study on ٦٠ patients scheduled for total knee replacement under spinal anesthesia with bupivacaine and they reported that the duration of motor block was longer in the neostigmine group more than morphine group. The duration of sensory block was prolonged in the two groups but it was more prolonged in morphine group. They also reported that the overall satisfaction rating was better in neostigmine group with fewer side effects.

The current study found that adding ٠.٥ mg of neostigmine to LA prolonged post

operative analgesia and delayed the time to ١st analgesic request.

This is in agree with Almeida et al.,[١٩] in their study to evaluate the antinociceptive effect of different doses of intrathecal neostigmine(١ to ٥ mg) when added to ١٠٠ µg morphine with bupivacaine for spinal anesthesia on ٦٠ women under-going gynecological surgery under spinal anesthesia, and they reported that neostigmine doubled the time of ١st rescue analgesic dose and decreased analgesic consumption in ٢٤ hours without increasing the incidence of adverse effects.

Nakyama et al.,[٢٠] found that epidural neostgmine ١٠µg/kg added to ١٠mg bupivacaine prolonged the time to ١st analgesic request in ٤٥ women under-going hysterectomy under general anesthesia without increased side effects.

Bone et al.,[٢١] in their study on ٣٤ patients undergoing to hand surgery under axillary plexus block and they found that adding ٠.٥mg neostigmine to LA mixture improved postoperative analgesia in axillary brachial plexus block.

Gentili et al.,[٢٢] in their study to compare between the analgesic effect of intra-articular clonidine ١٥٠ µg and neostigmine ٥٠٠µg in patients under-going knee arthroscopy, found that both of them produce equipotent post-operative analgesia with no side effects.

Turan et al.,[١٠] examined the effect of adding ٠.٥ mg neostigime to prilocaine in intravenous regional anesthesia in ٣٠ patients scheduled for hand surgery and they found that neostigmine accelerated onset time of sensory and motor block, prolonged duration of the block, enhanced depth of anesthesia, increased the time to the ١st analgesic request without serious side effects.

On the other hand McCartney et al.,[٢٣], evaluated the effect of ١mg neostigmine added to lidocaine ٠.٥٪ in intravenous regional anesthesia for hand surgery and they did not found any significant advantage of adding neostigmine to the local anesthetic on the block characters or on postoperative analgesia. These results may be explained by the high incidence of anesthetic technique failure in their study.

Limitation of the study: This study has is limited by the lack of similar researches using neostigmine in peribulbar anesthesia. It is recommended to do further evaluation of peribulbar neosti-gmine in other operations such as cataract and viteroretinal surgeries.

Conclusion

This study concluded that addition of ٠.٥ mg neostigmine to local anesthetic solution in peri bulbar anesthesia accelerated the onset of sensory, motor block, time for adequate conditions to start surgery, prolonged the duration of sensory and motor block, delayed the time of ١st analgesic request, increased satisfaction of the patients, and improved quality of surgical conditions without any side effects.

Conflict of interest: The authors declared that no conflict of interest. The fund of the research was from the university budget.

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