ORIGINAL RESEARCH

Effectiveness of transdermal nitroglycerine patch in improving analgesia of intrathecal neostigmine following the hysterectomies under bupivacaine spinal anesthesia

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ABSTRACTS

Introduction: Pain is a dehumanising sensation that diminishes the essence of a person. Pain is described as an unpleasant sensory and emotional experience linked to real or possible harm to body tissues or described in terms of such harm. There are various choices for managing pain after surgery, such as medications that affect the whole body (such as opioids and non-opioids), as well as treatments that target specific regions. Neostigmine is a commonly used drug to reverse the effects of neuromuscular block. Its ability to provide pain relief after surgery was initially reported by Naguib and Yaksh et al in 1994.**Material and methods:** The research was carried out in the anesthesia department of tertiary care hospitals affiliated with medical institutions in Haldia for a duration of one year. The study was carried out on 150 patients between the ages of 30 and 60 who were scheduled for hysterectomies. These patients had ASA grade I and II and gave their informed consent. Patients were divided into three groups, with each group consisting of 50 patients.**Conclusion:** The findings indicate that neostigimise prolongs the duration of pain relief provided by bupivicaine. Additionally, the use of transdermal nitroglycerine further enhances this postoperative pain relief. However, nitroglycerine alone does not possess any inherent analgesic properties. The use of intrathecal neostigmine and fentanyl in combination with bupivacaine resulted in a significant increase in postoperative pain relief compared to the control group, as well as the groups that received only bupivacaine and fentanyl or neostigmine.

INTRODUCTION

Pain is a dehumanising sensation that diminishes the essence of one's being. Pain is described as an unpleasant sensory and emotional experience linked to real or possible harm to tissues or described in terms of such harm. Pain comes from the Latin word "poena", which meaning penalty or punishment. Pain is no more regarded as a penalty or punishment. Alleviating pain is one of the primary objectives of medical science. Anaesthesia primarily focuses on alleviating pain during surgical procedures.[1]Any knowledge gained in this area should be applied throughout the postoperative period.> Intense pain after surgery is a widely recognised negative outcome and can be distressing for patients.[2]Although new pain relievers have been introduced, the progress in providing postoperative pain management still relies on enhancing the administration of current medications to patients.[3]The international organisation for the examination of pain has defined pain as an unpleasant and emotional experience linked to real or potential harm to body tissues or described in terms of such harm.[4]

There are various choices for managing pain after surgery, such as medications that affect the whole body (such as opioids and non-opioids) and treatments that target specific regions. The effectiveness of intravenous opioids is usually restricted by the occurrence of tolerance or side effects associated with opioids. Intravenous opioids are frequently employed to manage post-operative pain that ranges from moderate to severe.[5]Neuraxial and peripheral methods can offer better pain relief compared to systemic medications. Spinal anaesthesia, a frequently used method in the field of anaesthesia, has had a turbulent journey over its relatively brief existence. Particularly

between 1900 and 1940, it saw periods of strong support, doubt, and even outright criticism. In 1957, Ekenstemsynthesised bupivacaine and noted that it had a longer duration of action and lower toxicity compared to lignocaine.[6]The phrase "Spinal anaesthesia" was coined by Leonard Corning, a neurologist from New York, in 1885.[7]

Surgery causes significant tissue damage and it is common for patients worldwide to experience pain after the operation. Interestingly, despite the efforts made to minimise pain and stress during the surgery, patients are often left to manage their own discomfort during the recovery period. Neuraxial blockade is a possible solution for managing post-operative discomfort. Neostigmine is a commonly used drug to reverse the effects of neuromuscular block. Its ability to provide pain relief after surgery was initially reported by Naguib and Yaksh et al in 1994.[8]It prevents the breakdown of acetylcholine (a natural neurotransmitter) which has been proven to relieve pain by promoting the production of nitric oxide [NO] in the spinal cord.[9]It inhibits the function of both true and pseudocholinesterase, which increases the buildup and attachment of acetylcholine at different cholinergic locations.[10]However, a larger amount of neostigmine has been found to cause many undesirable symptoms such as nausea, vomiting, and so on. On the other hand, smaller dosages of neostigmine do not exhibit significant analgesic properties. In order to decrease the amount of neostigmine and enhance its pain-relieving effect, various substances such as clonidine, opioids, and transdermal nitroglycerine patch have been included with it. The transdermal nitroglycerine serves as a supplier of nitric oxide (NO).Nitric oxide functions as a second messenger in the central nervous system and has a significant impact in pain management. NO increases intracellular cGMP levels by activating the enzyme guanyl cyclase. The Nitric Oxide-cyclic GMP pathway in endothelial cells is responsible for both acetylcholine-induced vasodilation and acetylcholine-induced pain relief.[11]

MATERIAL AND METHODS

The research was carried out in the anesthesia department of tertiary care hospitals affiliated with medical institutions in Haldia for a duration of one year. The study was carried out on 150 patients between the ages of 30 and 60 who were classified as ASA grade I and II and scheduled for hysterectomies, after gaining their informed consent. Patients were divided into three groups, with each group consisting of 50 patients.

Group C: Patients received 15mg [3ml] of intrathecal bupivacaine.

Group N: Patients received 15mg [3ml] of intrathecal bupivacaine and 25µg [1ml] of neostigmine.

Group P: Patients, in addition to 15mg [3ml] of intrathecal bupivacaine and 25µg [1ml] of neostigmine, received transdermal NTG patch [5mg/24hours] at chest wall in non-anaesthetized area 15 minutes after intrathecal administration of drug solution.

Visual analogue scale [VAS] was utilised as a pain rating system, with 0 representing no pain and 10 representing the most severe pain. Following the administration of Ringer Lactate at a dose of 10ml/kg to the patients, spinal anaesthesia was carried out at the L3-L4 level using a 25 gauge Quincke needle. A volume of 4ml of medication was injected into the intrathecal space.

Sensory level was evaluated using a pinprick. Blood pressure was measured every 5 minutes during the surgery. An injection of ephedrine 6mg intravenously was administered when the systolic blood pressure dropped below 15% of the baseline. Pulse rate and oxygen saturation levels were monitored continually. Treatment was administered for a heart rate below 60 beats per minute with an intravenous injection of atropine 0.2mg. Vomiting during surgery was managed with an intravenous injection of 10mg of Metoclopramide. After the surgery, the VAS score was utilised to evaluate the pain in the participants at 30-minute intervals. Patients received further pain relief when their pain level on the Visual Analogue Scale (VAS) reached 4. Additional negative symptoms such as vomiting, nausea, drowsiness, bradycardia, hypotension, perspiration, headache, and palpitation were also observed. Pentazocine 30 mg was given intramuscularly as a rescue pain reliever. The length of pain relief was measured from the moment the medicine was given through an injection into the spinal canal until the VAS score reached 4.

RESULT

Table 1: Age distribution

Age group	Group C		Group N		Group P	
	No:	%	No:	%	No:	%
Upto 40 years	7	14	17	34	18	36
41-50 years	28	56	25	50	20	40
51-60 years	15	30	8	16	12	24
Total	50	100	50	100	50	100
Range	36-56 years		34-56 years		38-60 years	
Mean	46.8 years		46.2 years		46.9 years	
‘p’ value	>0.05		>0.05		>0.05	

Table- 2: Distribution of weight among the three groups

Group	Weight (in kg)		
	Range	Mean	SD
Group C	44-68	54.6	6.6
Group N	46-62	54.1	5.1
Group P	42-65	52.3	6.12
'p' value	0.9238 Not significant		

Table -3: Duration of surgery

Group	Duration of surgery in minutes		
	Range	Mean	SD
Group C	54-129	91.5	18.3
Group N	62-123	86.5	19
Group P	62-122	88.3	19.2
'p' value	0.3896 Not significant		

There is no statistically significant difference between duration of surgery among the three groups.

Table 4: comparison of three regimensin pulse rate

Pulse rate	Pulse rate						'p' value between groups			
	Group C		Group N		Group P		C,N&P	C&N	C&P	N&P
	Mean	SD	Mean	SD	Mean	SD				
Pre operative	90	10	91.6	11.9	90.3	13.6	0.8267 Not significant	0.6702 Not significant	0.593 Not significant	0.7823 Not significant
Intra operative	90.8	11.4	87.2	11.2	86.8	13.4	0.1936 Not significant	0.0823 Not significant	0.213 Not significant	0.989 Not significant
Post operative	88.6	10.8	88.6	11.8	86.6	13.2	0.8236 Not significant	0.6805 Not significant	0.6157 Not significant	0.6616 Not significant
Decrease	4	2.8	3.8	5.2	3.8	7.6	0.8724 Not significant	0.5609 Not significant	0.6504 Not significant	0.9756 Not significant

Table -5: Changes in Mean Arterial Pressure among the three groups

MAP	MAP of						'p' value between groups			
	Group C		Group N		Group P		C,N&P	C&N	C&P	N&P
	Mean	SD	Mean	SD	Mean	SD				
Pre operative	90.6	5.4	90.6	5.6	89.8	7.2	0.5267 Not significant	0.4672 Not significant	0.583 Not significant	0.332 Not significant
Intra operative	86.8	5.9	86.2	5.6	84.8	6.9	0.1936 Not significant	0.9823 Not significant	0.243 Not significant	0.1189 Not significant
Post operative	86.6	5.8	88.6	5.2	86.6	6.8	0.8263 Not significant	0.5405 Not significant	0.9867 Not significant	0.5961 Not significant
Decrease	4	1.8	3.8	4.8	3.8	2.4	0.129 Not significant	0.9629 Not significant	0.1286 Not significant	0.5276 Not significant

Table- 6: Comparison of Duration of Analgesia

Group	Duration of Analgesia in minutes		
	Range	Mean	SD
Group	122-182	152.3	16.1
Group	181-252	212.2	23.2
Group	205-395	315.2	47.3

'p' value between Groups C,N & P	0.0001 Significant
C&N	0.0001 Significant
C&P	0.0001 Significant
N&P	0.0001 Significant

Table -7: Adverse effects

	GROUP P	GROUP N	GROUP C
NAUSEA	9	9	3
VOMITING	7	8	2
HYPOTENSION	4	3	4
BRADYCARDIA	3	4	2

Table -8: Comparison of adverse effects

Group	Nausea and Vomiting			
	Yes		No	
		%		%
Group C	4	11.9	24	89.5
Group N	16	58.4	12	43.2
Group P	15	54.2	13	47.2
'p' value between Groups				
C & N	0.0238 – Significant			
C & P	0.046 – Significant			
N & P	0.7922 - Not significant			

DISCUSSION

Different medications have been tested in the subarachnoid area, together with local anaesthetics, in order to enhance the length of post-operative pain relief. Neostigmine, a type of cholinesterase inhibitor, is one of these adjuvants. Although neostigmine has been found to cause a longer period of pain relief, it has also been linked to some undesirable side effects, namely nausea and vomiting, especially when taken in higher amounts. In order to decrease the occurrence of negative effects and extend the duration of pain relief after surgery, several substances have been utilised in combination with neostigmine. The objective of this study was to comprehensively examine the existing evidence on the pain-relieving effects of combining intrathecal neostigmine with a transdermal nitroglycerine patch during bupivacaine spinal anaesthesia. The analgesic action of neostigmine, when injected intrathecally, is achieved through the release of acetylcholine in the spinal cord. Elevated levels of acetylcholine caused by surgical stimuli and acetylcholine protected from the anticholinesterase effects of intrathecal neostigmine, attach to nicotinic and muscarinic nerve endings in the spinal cord. Research has shown that cholinergic agonists exert inhibitory effects on neurons in the spinal dorsal horn, including the spinothalamic tract.This indicates that a spinal cholinergic system has a significant inhibitory function in the regulation of pain pathways.

This study aimed to determine if the pain-relieving effect of intrathecal neostigmine can be increased by transdermal NTG, which serves as an external supply of nitric oxide. In this investigation, the researchers examined the length of time that pain relief lasted, starting from when the medicine was given through an injection into the spinal cord until the VAS score reached 4. In terms of statistical analysis, patients in Group C reported experiencing pain earlier compared to the other groups, with a period of analgesia lasting 2.5 hours. There was a statistically significant delay in the start of discomfort in Group N and Group P. Our investigation shows comparable statistical values.

Lauretti, Gabriela R. and colleagues conducted a trial in 2000 to investigate whether combining transdermal nitroglycerine with a low dose of intrathecal neostigmine would improve pain relief in patients undergoing gynecologic surgery with spinal anaesthesia.[12]The researchers found that neither the use of 5 μg neostigmine alone through intrathecal administration nor the use of transdermal nitroglycerine alone (5 mg/day) caused a delay in the time it took for the first rescue analgesics to be administered. However, when both neostigmine and nitroglycerine were used together, they provided an average of 550 minutes of effective postoperative pain relief following vaginoplasty. There was no notable variation in the occurrence of negative effects. The researchers proposed that the use of transdermal nitroglycerine with the central cholinergic drug neostigmine would have a synergistic effect on pain relief, which aligns with the results of my study. The larger dose of neostigmine used in my investigation may have contributed to the increased occurrence of side effects.

Gurvinder Kaur, NarjeetOsahan, and Lalita Afzal conducted a study in 2007 to investigate the impact of a transdermal NTG patch (5mg/24hours) on the combination of intrathecally administered

neostigmine (5μg) and 15mg bupivacaine, as well as the occurrence of adverse effects.[13]The researchers discovered that the typical length of pain relief in the group that received intrathecal neostigmine (Group I) was 6.5 hours, whereas in the group that received both neostigmine and a transdermal nitroglycerine patch (Group II), it was 9.10 hours. The duration of pain relief was substantially longer in participants in Group II compared to Group I. The occurrence of nausea was greater in Group I compared to Group II. The increased pain relief from injecting neostigmine into the spinal canal, combined with applying NTG to the skin, in this research is consistent with my own investigation. The larger dose of neostigmine used in my trial may have contributed to the increased occurrence of nausea and vomiting.

Fareed Ahmed and colleagues (2010) conducted a study to investigate the impact of a transdermal nitroglycerine patch on intrathecal neostigmine.[14]Patients were divided into four groups. Group I was given 15 mg of bupivacaine through intrathecal administration. Group II received 15 mg of bupivacaine along with 5 μg of neostigmine through intrathecal administration. Patients in Group III were given 15 mg of bupivacaine along with 1 ml of normal saline through intrathecal administration, as well as a transdermal NTG patch (5 mg/24 hours). Patients in Group-IV were administered 15 mg of bupivacaine together with 5μg of neostigmine by an intrathecal route. Additionally, they were given a transdermal NTG patch with a dosage of 5 mg every 24 hours. The average duration of pain relief was 202.2 minutes, 407.6 minutes, 207.8 minutes, and 581.6 minutes in Group [1], Group [II], Group [III], and Group [IV] accordingly.

The group that received intrathecal bupivacaine and transdermal nitroglycerine patch was excluded from my study since previous research has shown that transdermal nitroglycerine patch does not have its own analgesic capability. The increase in pain relief caused by injecting neostigmine into the spinal cord and the strengthening of the pain-relieving effect of neostigmine by using a transdermal NTG patch are consistent with the results of my investigation. The lack of alteration in perioperative hemodynamic measures seen in this study is likewise consistent with my findings. The larger dose of neostigmine used in my trial may have led to an increase in the occurrence of nausea and vomiting.

CONCLUSION

The findings indicate that neostigimise prolongs the duration of bupivicaine-induced analgesia, and transdermal nitroglycerine enhances this postoperative analgesic effect. However, nitroglycerine alone does not possess any analgesic properties. The study indicates that there is a noticeable delay in the time when the first rescue pain relief is needed, as well as a reduced need for the total number of rescue pain relief medications in patients who were given both clonidine and the nitroglycerine patch, compared to patients who only received intrathecal clonidine.Additionally, patients who got both clonidine and the nitroglycerine patch experienced longer pain relief, a longer period of reduced motor function, and a smaller number of these effects compared to individuals who only received intrathecal clonidine. The use of intrathecal neostigmine and fentanyl in combination with bupivacaine resulted in a significant increase in postoperative pain relief compared to the control group, as well as the groups that received only bupivacaine and fentanyl or neostigmine.

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