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EFFECTS OF THORACIC EPIDURAL CLONIDINE AND/OR MAGNESIUM SULPHATE AS ADJUVANTS TO BUPIVACAINE AND MORPHINE FOR POSTOPERATIVE PAIN RELIEF AFTER CARDIAC SURGERIES

By

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ABSTRACT

Background: Postoperative pain after cardiothoracic surgery is one of the most severe types of postoperative pain due to sternotomy or muscle-dividing incision of the chest wall. It leads to inability to cough and to maintain their functional residual capacity which leads to retention of secretion and pneumonia. So, proper control of post-operative pain improves the patient's outcome.

Objective: The present study was designed to evaluate the quality and efficacy of post-operative analgesia of clonidine and/or magnesium sulphate when added to bupivacaine and morphine in thoracic epidural analgesia for cardiac surgery.

Patients and methods: A prospective, double blind randomized study was carried out on eighty patients classified into four equal groups, i.e. *group I (control)*: received 5 ml bupivacaine (0.5%) + 2mg morphine sulphate (to be diluted to 10 ml of 0.9% saline), *group II:* received the same solution for group I + 50 mg of magnesium sulphate, *group III*: received the same solution for group I + 75 ?g clonidine and *group IV:* received the same solution for group I + 50 mg magnesium sulphate and 75 ?g clonidine. All patients received the first postoperative analgesic dose through the epidural catheter just after being transferred to postoperative intensive care unit (ICU). According to the scheduled intervals, heart rate, mean arterial blood pressure, arterial blood gases, as well as visual analuge score (VAS) were recorded for 24 hours postoperatively. Duration of analgesia, frequency of top up analgesic doses and surgical stress response parameters (serum blood glucose and cortisol) were also recorded.

Results: Groups III and IV recorded prolonged duration of analgesia, decreased requirements of bupivacaine and morphine, with improvement of pain relief. All results of group III indicated that clonidine was more effective than magnesium sulphate when used as adjuvant for epidural analgesia for postoperative pain management.

Conclusion: Epidural clonidine prolonged the duration of analgesia, decreased the local anesthetic requirement and improved quality of pain relief, when added to bupivacaine and morphine for postoperative analgesia after cardiac surgery when compared to magnesium sulphate that had no beneficial effect as an adjuvant.

Key words: Clonidine, magnesium, thoracic epidural, cardiac surgery.

INTRODUCTION

Postoperative pain after cardiothoracic surgery is one of the most severe types of pain as the surgery involves sternotomy or muscle-dividing incision of the chest wall, which results in severe pain during

respiratory movement. As a result, the patients will not be able to cough and to maintain their functional residual capacity which may lead to retention of secretion and pneumonia. So, proper control of post-operative pain, in addition to providing comfort for the patient, facilitates early weaning and extubation, chest physiotherapy, effective expectoration, early ambulation and leads to shorter length of hospital stay which means overall improvement of patient's outcome ***(Arif et al., 2003).***

The thoracic epidural analgesia was selected as a good choice for postoperative pain relief to avoid not only the side effects of non-steroidal anti-inflammatory drugs (NSAIDs) as gastrointestinal and renal complications, but also the respiratory depression due to parenteral opioids. Safety, efficiency, effectiveness and long duration of analgesia were considered especially with long acting local anesthetics or addition of opioids as adjuvant to local anesthetics ***(Grape and Tramer, 2007).***

Addition of other drugs in neuraxial analgesia as clonidine and magnesium sulphate was studied to improve quality of analgesia. Magnesium sulphate has an important role in pain relief because it acts as a physiological blocker for calcium channels which inhibits calcium influx into the cell via a noncompetitive block of the N-methyl- D-aspartate (NMDA) receptor channels ***(Begon et al., 2002 and Hussien, 2011).***

Clonidine (centrally acting partial α-$_2$ adrenergic agonists) was used primarily for its antihypertensive effects (α_2 to α_1 receptor ratio of 200:1). This decrease in central sympathetic outflow does not affect baroreceptor reflexes, therefore not causing orthostatic hypotension ***(Moss and Renz, 2005)***. Clonidine inhibits voltage gated Na^+ channels and suppresses the generation of action potentials. So, it inhibits the activity of second-order neurons and attenuates the input from peripheral nociceptive A and C fibers which carry an important role in pain relief ***(Roelants, 2006).*** Alpha-2 agonists like clonidine causes analgesia by non-opioid mechanism as an alternative agent to opioid. It was stated that clonidine neither blocks proprioception, like local anesthetics, nor causes respiratory depression, itching, nausea and vomiting like opioids. When given epidurally with local anesthetics it increases their potency. However, it was also causing hypotension, bradycardia and sedation ***(Shobhana et al., 2010).*** The prolongation of the motor block of neuraxial anesthetics may be the result of binding of α_2 adrenoreceptor agonists to the motor neurons in the dorsal horn ***(Al Ghanem et al., 2009).***

PATIENTS AND METHODS

This prospective, double blind randomized study was carried out at the cardiothoracic surgery department, Al-Azhar University Hospitals after ethical committee approval. Simple random selection and random allocation technique was used for randomization. Informed written consent was obtained from eighty patients of both sexes undergoing cardiac surgery for various indications. Patients who had allergy to local anesthetics, local infection at or near the needle insertion site, age below 18 years or above 60 years, history of hepatic, renal failure, hemorrhagic disorders or who refused the technique were excluded from the study.

Eighty patients were randomly allocated into four equal groups, i.e. *group I (control group)* received 5 ml bupivacaine (0.5%) + 2mg morphine sulphate (diluted to 10 ml of 0.9% saline), *group II* received the same solution for group I + 50 mg magnesium sulphate, *group III* received the same solution for group I + 75 ?g clonidine, and *group IV* received the same solution for group I + 50 mg magnesium sulphate and 75 ?g clonidine. All patients received the first analgesic dose through the epidural catheter just after patient transfer to postoperative intensive care unit (ICU). All patients were assessed prior to surgery by proper history, clinical examination, laboratory investigations and specific investigations as required for surgery.

An 18G intravenous cannula was inserted, then 0.04 mg/kg midazolam was administered as premedication 10 min before arrival to operating theater.

All patients were monitored (intra-operatively and in the ICU) by pulse oximetry, five leads ECG, noninvasive and invasive arterial blood pressure, capnography for end-tidal CO_2, temperature, central venous pressure (CVP), activated clotting time (ACT), arterial blood gases (ABG) and foley's catheter for monitoring of urine output. All studied patients were trained on how to use visual analogue scale (VAS) before the procedure.

Vital data (heart rate, blood pressure, arterial blood gases, $EtCO_2$ and oxygen saturation) and serum cortisol and glucose levels were recorded as a base line before induction of anesthesia.

The epidural catheter was inserted at the T4-5 or T5-6 interspace. The mixture solution (prepared by a doctor not involved in the study) was injected through the epidural catheter according to the randomization list. After that, all patients received a standard general anesthetic technique (3 μg/kg fentanyl, 2 mg/kg propofol and 0.1 mg/kg pancuronium as induction doses followed by tracheal intubation). Isoflurane (0.5-1%) was used for maintenance all over the operation.

At the end of operation, all patients were transferred to ICU for postoperative care for 24 hours (at least). They received the first postoperative analgesic dose through the epidural catheter and the base line (0 time for data recording) hemodynamic data were recorded. The epidural top up doses were given once a 20% increase of mean arterial blood pressure or heart rate had been recorded, before extubation or according to patients request (VAS >40) after extubation.

Heart rate, mean arterial blood pressure, arterial blood gases were recorded hourly for the first six hours, every 2 hours for the second six hours then every four hours through the rest 12 hours postoperatively.

Duration of analgesia in hours (time after drug injection to the next required dose), frequency of top up analgesic doses and stress response parameters (serum glucose and cortisol levels measured at 6 hours after skin incision) were recorded. Side effects like nausea, vomiting, hypotension, late respiratory depression (after extubation), or local anesthetic toxicity were recorded.

The patients were given 1-2 µg/kg fentanyl intravenously to relieve pain if unsatisfactory postoperative analgesia was noted after supplementary epidural injection.

Data were analyzed using SPSS version 18.0. Qualitative data were expressed as frequency and percentage, while the quantitative data were expressed as mean ± standard deviations (SDs). Statistical comparisons were performed by ANOVA test. Chi-square (X^2) test was used in order to compare proportions between two qualitative parameters. Post-hoc Tukey test was used for multiple comparisons. A probability value <0.05 was considered statistically significant.

RESULTS

The present study included 80 patients divided into 4 equal groups. The demographic data (age, sex and operative procedures) denoted no statistical significant difference between groups (P value > 0.05) as shown in table 1.

Table (1): Demographic data.

Groups / Parameters	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)	P value
Gender: Male	9 (45%)	14 (70%)	17 (85%)	13 (65%)	0.062
Female	11 (55%)	6 (30%)	3 (15%)	7 (35%)	
Age (years)	35.2±15.2	36.7±15.8	36.9±11.4	39.2±17.8	0.876
Operative procedures					
AVR	7 (35%)	6 (30%)	7 (35%)	10 (50%)	0.444
CABG	6 (30%)	4 (20%)	3 (15%)	6(30%)	
MVR	7 (35%)	10 (50%)	10 (50%)	4 (20%)	

AVR: aortic valve replacement, CABG: coronary artery bypass graft, MVR: mitral valve replacement

As regard the heart rate, a statistically significant decrease from baseline values was recorded in groups III and IV compared with groups I and II. Tachycardia was recorded after 13 hours from admission to ICU in groups III and IV. On the other hand, it was recorded after 9 hours in groups I and II (Fig 1).

As regard the mean arterial blood pressure (figure 2), there was no statistical significant differences between groups all over the postoperative period. No recorded differences between groups as regard oxygen saturation, respiratory rate and arterial blood gases (ABG) all over the postoperative period (Fig. 2).

Figure (1): Heart rate changes.

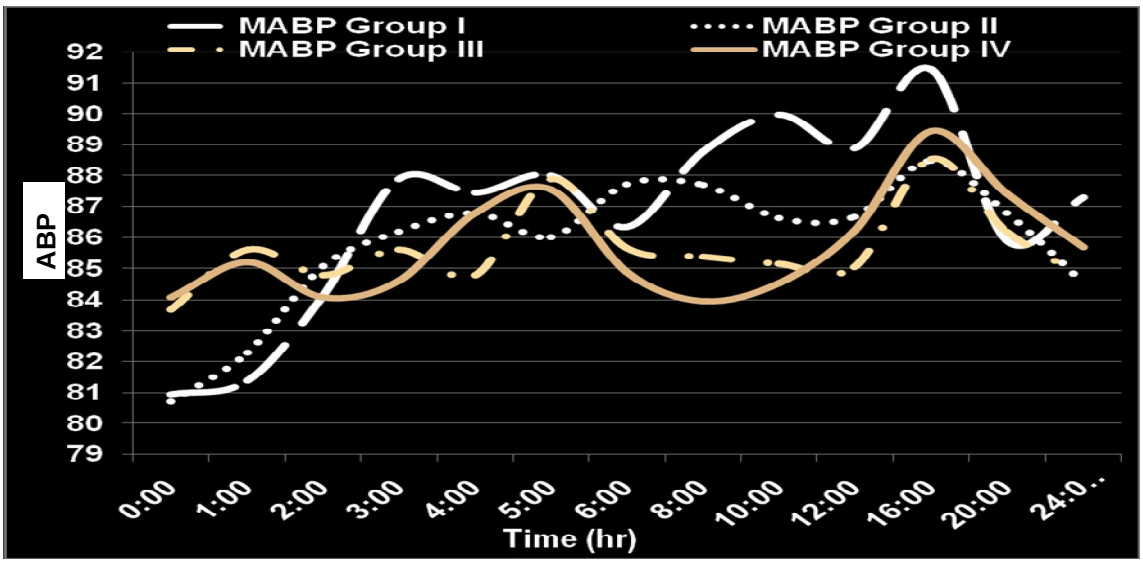

Figure (2): Mean arterial blood pressure changes (MABP).

As regard the duration of analgesia of the postoperative supplementary epidural doses in ICU (table 2), groups III and IV recorded statistical significant increase in duration of analgesia (about 13 to 14 hours), compared to 9 to 10 hours in groups I and II which was indicated mainly by the difference in the heart rate and patient request according to VAS assessment ≥ 40.

Table (2): Duration of postoperative analgesia.

Groups / Parameters	Group (I)	Group (II)	Group (III)	Group (IV)	P value
Duration of analgesia (hr.)	10±1.9	10±1.8	15.5±0.7*	14.8±0.4*	<0.001

Data were expressed as mean±SD, ANOVA test was done.

As regard the total number of doses, groups III and IV recorded statistically significant lower number of doses. Ten (50%) patients in group III and 7 (35%) patients in group IV were satisfied with the first dose while 10 (50%) patients in group III and 13 (65%) patients in group IV requested the second dose to reach the targeted level of analgesia. No one of either group III or IV request the 3rd dose as shown in table (3). In both groups I and II, it was recorded that 13 (65%) and 10 (50%) patients 'respectively' asked for the third dose to reach the target level of analgesia, while, no one of either group I or II was satisfied with the first dose.

Table (3): Number of patients satisfied with postoperative supplementary analgesic doses**.**

Groups / Number of doses	Group (I) (n= 20)	Group (II) (n= 20)	Group (III) (n= 20)	Group (IV) (n= 20)	P Value
Number of patients satisfied with the first dose in ICU	0 (0%)	0 (0%)	*10 (50%)	*7 (35%)	0.001
Number of patients satisfied with second dose in ICU	7 (35%)	10 (50%)	*10 (50%)	*13 (65%)	
Number of patients asked for third dose in ICU	*13 (65%)	*10 (50%)	0 (0%)	0 (0%)	

Data were expressed as frequency and percentage; x^2 – Chi-square test was done
*significant when compared to control group

As regard the bupivacaine and morphine consumption, groups III and IV demonstrated a statistically significant lower consumption (about 40%) in comparison to groups I and II. The statistical analysis demonstrated that there is no effect for magnesium on bupivacaine and morphine consumption (Table 4).

Table (4): Bupivacaine and morphine consumption**.**

Groups / Parameters	Group (I) (n=20)	Group (II) (n= 20)	Group (III) (n= 20)	Group (IV) (n= 20)	p-value
Bupivacaine (mg)	66.25±12.23	61.25±12.76	37.50±12.82*	41.25±12.23*	<0.001
Morphine (mg)	5.30±0.98	4.90±1.02	3.00±1.03*	3.30±0.98*	<0.001

*significant when compared to control group, ANOVA test was done.

As regard serum cortisol and glucose levels, all studied groups showed statistical significant increase (without clinical effects) in cortisol and glucose

levels in the serum of blood samples taken 6 hours after skin incision compared to preoperative values. On the other hand, group III and IV showed better results as regard the attenuation of stress response. It was reflected as reduction in cortisol and glucose levels in the blood samples taken 6 hours after skin incision in group III and IV compared to group I and II (Table 5).

Table (5): Comparison between groups as regard serum cortisol and glucose levels**.**

Parameters \ Groups		Group (I)	Group (II)	Group (III)	Group (IV)	P value
Serum cortisol (ug/dl)	Preoperative	18.2±10.2	13.6±3.2	11.1±0.7	12.8±1.3	0.07
	6 hr post skin incision	34.6±5.5	27.2±4.6	20.3±1.9	23.5±9.3	<0.001
Serum glucose (mg/dl)	Preoperative	141±37.3	113.7±16.5	134.7±16.3	120±231.1	0.6
	6 hr post skin incision	178.2±21.3	187.1±24.7	146.2±17.2	147.4±15.2	<0.001

Data were expressed as mean ±SD, ANOVA test was done followed by Post-hoc Tukey test for multiple comparisons.

As regard the side effects, no recorded side effects (nausea, vomiting, hypotension, late respiratory depression (after extubation) or local anesthetic toxicity) in any of the studied patients in all groups.

DISCUSSION

Adequate analgesia without major side-effects is the aim of postoperative analgesic management. The most common drugs used for postoperative analgesia are opioids, but the large doses may be associated with respiratory depression, urinary retention and pruritus ***(Ruetsch et al., 2001*** and ***Bilir et al., 2007).***

As regard the heart rate, a statistically significant decrease (less than 90 beats/min) was recorded in patients who received clonidine either alone or with magnesium. While the mean heart rate in patients who received magnesium sulphate alone or in control group were higher than 90 beats/min. On the other hand, the inter-group comparison showed no beneficial effect for addition of magnesium sulphate. These results were comparable to that of ***Shobhana et al. (2010),*** who reported bradycardia with epidural clonidine that was attributed to decreased sympathetic nerve activity.

Arterial blood pressures were comparable among all patients of the studied groups in the current study, which contradict with results of **Laurent and Jean-Claude (2003),** who found moderate increase of the heart rate and systolic blood pressure with decreased plasma concentrations of epinephrine and norepinephrine after intubation in patients treated with magnesium sulphate. In the current study (due to the nature of surgery), all patients were admitted to the ICU for post-operative care. They (routinely) receive vasopressors and

inotropic support (50-100 nanogram/kg/ min epinephrine) as required with monitored fluid replacement that minimized the hypotension with any epidurally administered drugs and this may describe the differences between the studies.

Vidhi et al. (2013) reported that there is no significant hypotension in their studied patients as regards the effect of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery, this come with the results of the current study. This was attributed to the use of small doses of α_2 agonists with local anesthetics and these doses of adjuvants did not affect the near maximal sympatholysis caused by local anesthetics**.**

In 2010, **Tanmoy et al.** studied the effect of magnesium sulphate versus clonidine as adjuvant to epidural bupivacaine for postoperative pain in patients undergoing lower abdominal and lower limb surgeries, they reported statistically insignificant arterial blood pressure changes among the groups and this result reinforces the results of the current study**.**

Actually, the current study recorded insignificant changes between control group and group II as regard duration of analgesia and consequently total drug consumption. 50% of patients of group II and 65% in control group asked for the third top up epidural dose to reach the required analgesic level (VAS < 40). This may be attributed to the analgesic effect of magnesium which is directly related to CSF concentration as described by **Arcioni et al. (2007)** and ***Yousef & Amr (2010).*** They studied the effect of 500 mg of magnesium sulphate and fentanyl when added to epidural bupivacaine in elective caesarean section and reported delayed onset of post-operative pain. These results may interfere with the results of the current study which used only 50 mg of magnesium sulphate that did not achieve a significant effect on duration of analgesia or local anesthetic consumption because of its poor penetration to the intrathecal space.

Kanazi et al. (2006) reported that the effect of 3 micrograms of dexmedetomidine and 30 micrograms of clonidine intrathecally produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation when used in equipotent doses. In the current study, we used clonidine as an α_2 agonist and not dexmedetomidine because of its availability.

Vaibhav *et al.* (2014) studied the effect of magnesium or dexmedetomidine on epidural bupivacaine in lower limb surgeries. They found that the minimal side effects and excellent postoperative analgesia of epidural dexmedetomidine make it an attractive adjuvant to epidural bupivacaine in prolonged surgeries. Magnesium sulfate, administered epidurally, also prolongs the duration of analgesia, but less than epidural dexmedetomidine. **Wolf et al. (2007),** supported the results of the current study as regard postoperative analgesia as they stated that clonidine can prolong the duration of peripheral nerve blocks. It can be used effectively as an adjuvant to opioids and local anesthetics to treat acute and chronic pain.

As regard laboratory assessment of stress response in the present study, we found no beneficial effect of adding magnesium as it did not protect our patients from rise of serum cortisol and blood glucose. On the other hand, clonidine either alone or with magnesium showed better results as regard stress response attenuation.

The current study recorded no side effects {nausea, vomiting, hypotension, late respiratory depression (after extubation) or local anesthetic toxicity} in the four groups of patients. **Goodman et al.** (2006) reinforces the results of current study and reported that the larger doses (8.7gm and 9.6 gm) of magnesium inadvertently administered into epidural space do not cause any neurological injury. ***Ozalevli et al. (2005)*** confirms the safety of magnesium sulphate administered through epidural or intrathecal route.

Epidural clonidine when added to bupivacaine infusion for painless labor increases the analgesic effect without maternal or fetal side effects. This can be attributed to the non-opioid mechanism of clonidine, so, no respiratory depression, itching, nausea and vomiting like opioids. Administration of clonidine epidurally causes hypotension, bradycardia and sedation and increases potency of local anesthetics ***(Shobhana et al., 2010).***

CONCLUSION

Epidural clonidine was found to be superior to epidural magnesium in providing longer post-operative analgesia, less analgesic drug consumption and consequently less side effects with excellent attenuation of stress response evidenced by the lowest serum cortisol and glucose levels.

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طارق عبد السلام سليم

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خلفية البحث: تعد آلام ما بعد جراحات القلب والصدر من أشد الآلام وذلك لما تشمله هذه الجراحات من شق لعظمة القص أو عضلات القفص الصدرى. وقد يؤدى ذلك إلى عدم القدرة على السعال وعدم الحفاظ على القدرة الإحتياطية للجهاز التنفسى مما يؤدى إلى تجمع الإفرازات وحدوث إلتهابات الجهاز التنفسى. ولذلك يؤدى التحكم الجيد فى آلام ما بعد الجراحة إلى سرعة خروج المرضى من المستشفى.

الهدف من البحث: يقوم هذا البحث على أساس تقييم قدرة وكفاءة عقار الكلونيديين وسلفات الماغنيسيوم فى تسكين آلام ما بعد الجراحة عند إضافته لعقار البيوبيفاكيين والمورفين بالحقن المستمر خارج الأم الجافية في منطقة الصدر في جراحات القلب.

المرضى وطرق عمل البحث: أجريت الدراسة على ثمانين مريضا تم تقسيمهم إلى أربع مجموعات متساوية. *المجموعة الأولى* تم معالجة آلامهم باستخدام 5 ميلليتر من عقار البيوبيفاكين تركيز0.5 % مضافا إليه 2 ملليجرام مورفين ومكملا بمحلول الملح الطبيعى 0.9% حتى 10 ملليليتر، *والمجموعة الثانية* تمت معالجة آلامهم بإستخدام محلول المجموعة الأولى مضافا إليه 50 ملليجرام من سلفات الماغنسيوم، *والمجموعة الثالثة* تمت معالجة آلامهم بإستخدام محلول المجموعة الأولى مضافا إليه 75 ميكروجرام كلونيدين، *ثم المجموعة الرابعة* تمت معالجة آلامهم بإستخدام محلول المجموعة الأولى مضافا إليه 50 ملليجرام من سلفات الماغنسيوم مع 75 ميكروجرام من الكلونيدين. وقد تم إعطاء جميع المرضى جرعة مسكنة بمجرد دخولهم الرعاية المركزة بعد الخروج من العمليلت. وتبعا للجدول الزمنى المحدد يتم قياس النبض وضغط الدم وعمل غازات بالدم (بعينة شريانية) و نسبة الكورتيزول والجلوكوز بالدم قبل وبعد إجراء الجراحة ويتم أيضا متابعة درجة الألم وقياس مدة تسكين الألم ومعدل الإحتياج للمسكنات بعد إجراء الجراحة. وتتم متابعة حدوث المضاعفات.

النتائج: سجلت المجموعة الثالثة والرابعة إطالة زمن تسكين الألم بعد العملية وتقليل الكميات التى يحتاجها المريض من عقارى البيوبيفاكيين والمورفين مع تحسن فى حدة الألم. وقد إتضح من ذلك أن نتائج المجموعة الثالثة مرضية أكثر من المجموعات الأخرى، ويعنى ذلك أن الماغنسيوم ليس له أثرا كافيا عند إستخدامه كعقار إضافى فى الحقن خارج الأم الجافية في منطقة الصدر.

الإستنتاج: إستخدام عقار الكلونيدين عن طريق الحقن خارج الأم الجافية في منطقة الصدر يؤدى إلى اطالة مدة تسكين الألم وتقليل الجرعات المطلوبة وتقليل حدة الألم، ومن ثم تقليل الآثار الجانبية. لذلك يمكن إستخدام عقار الكلونيدين كعقار إضافى لعقار البيوبيفاكين والمورفين فى معالجة آلام جراحات القلب وذلك بالمقارنة بعقار سلفات الماغنسيوم والذى أثبتت الدراسة عدم جدواه.