

Comparison of propofol with thiopentone on the immune system

ALTINDIŞ M.¹, ÖZMEN S.², VATANSEV C.³, CERİ A.⁴, ŞENGİL A.Z.⁵

Departments of Microbiology and Clinic Microbiology¹, Anesthesia², General Surgery³, and Pediatrics⁴, School of Medicine, Selçuk University, Konya and Department of Microbiology and Clinic Microbiology⁵, School of Medicine, Celal Bayar University, Manisa

Objective This study was designed to compare the effect of thiopentone which was formerly and more commonly used, with propofol, a new anaesthetic agent, on cellular and humoral immunity and to choose the suitable one to patients according to the discovered results.

Methods By using TIVA technique first group patients were infused with propofol (2 mg/kg for induction, 6-12 mg/kg/hr for maintenance) and second group infused with thiopentone (3-5 mg/kg for induction, 7 mg/kg/hr for maintenance). Anaesthetic gas was not given. Many immunological (IgG, IgM, IgA, C3-C4, CD4 and CD8) and haematological (leucocyte, hct, Hb, blood smear and lymphocyte counts) testes were studied on samples obtained 30 min. before, 30 min. and 24 hr after the operation.

The immunoglobulin and complement were studied by radial immunodiffusion technique and CD4-CD8 were studied by immunofluorescence + monoclonal antibodies technique. The ppd test was also implemented before and after two days of anaesthesia.

Results In the study at postoperative 30 'th min decrease of IgG, IgM, IgA and C3 in the group used propofol and decrease of IgM, IgA and C4 in the group used

thiopentone were significant ($p<0.05$). At postoperative 24 'th hours increase of the IgG, IgM and C3 levels and decrease of IgA level in second group were significant ($p<0.05$). When compared the difference between the groups, difference of the decrease in the IgA level were significant ($p<0.05$).

When we reviewed cellular immunity interference, decrease of CD4, leucocyte and lymphocyte were significant in the both groups ($p<0.05$). At postoperative 24 'th hours while CD4 and CD8 levels and lymphocyte counts were significantly increasing in the first group, just lymphocyte count increase was significant in the second group ($p<0.05$). When compared the difference between the groups, decrease of the leucocyte and lymphocyte counts in the first group were significant ($p<0.05$). The postoperative second days ppd results were significantly decrease in both group ($p<0.05$). There was no difference between the groups.

Conclusion We conclude that both agents especially propofol have an immunosuppressive effect.

Key words Immune system, propofol, thiopentone

Introduction

Much of the immunological changes seen after a surgical operation is due to direct effect of some anaesthetic agents used or their contribution to operational trauma or endocrine response. Effect of the anaesthesia may differ due to breaking point of stress response, individual immune status, period and/or method of anaesthesia and chemical structure of anaesthetic agent while effect of operation on immune status is due to extension of the operation and individual stress response (1).

The immune system recognises foreign molecules and readily reacts against them. There is no definite tissue or organ in which the immune system is located. Components of the system are found nearly all parts of the body. They are normally stable whereas they migrate towards stimulus when a foreign molecule, a mutagenic or pathologic activity is detected (2).

Total intravenous anaesthesia (TIVA), which means transient loss of some reflexes and sense by loss of consciousness without interfering with vital functions at bulbus, become more common TIVA, of which hypnotic effect is provided by intravenous anaesthetic infusion, is an easy, rapid, secure and also economic way of anaesthesia (3,4,5).

Although it's new, propofol containing purified egg phosphatide, NaOH, soya bean oil and water is widely accepted as an anaesthetic agent (4,6,7,8) (Figure 1). Propofol is a short-term anaesthetic of which effect starts just after 30 seconds from application and patient is early and quickly arousable after anaesthesia. Additionally, it has very few postoperativar side-effects like nausea, vomiting and headache (9,10).

On the other hand thiopentone sodium(sodium ethyl-1 methyl butyl thiobarbiturate) is the most commonly used and to be experienced with, and is among the barbiturates with very short-term effectivity (11,12) (Figure 2).

Accepted for publication: 21 February, 1996

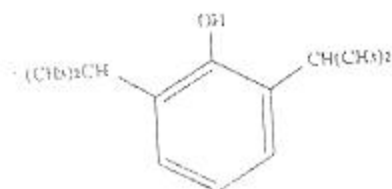


Figure 1. Chemical structure of propofol

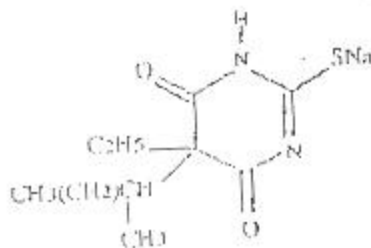


Figure 2. Chemical structure of thiopentone

Material and Method

With approval from our institutional ethic committee, this study was carried out on specimens were drawn 40 adult patients. Venous blood 30 minutes before and after the operation and 24 hours later. The blood specimens obtained were from those are taking no premedication, having no tumoral pathology or immune deficiency and being operated at S.U. Medical Faculty General Surgery division. The immunologic study was carried out at microbiology department.

The patients were separated into 2 groups. By means of infusion pump, propofol at a dose of 2-2.5 mg/kg infusion and 6-12 mg/kg/h maintenance was given to the first group by the TIVA while thiopentone at a dose of 3.5mg/kg infusion and 7mg/kg/h maintenance was given to the second group. Anesthetic gas wasn't used. As being muscle relaxant atracurium besilate and fentanyl for analgesia were applied on all patients.

The PPD test was performed on all patients before and after the 48 hours from operation and endurances were graded as 3 groups. Normal venous blood for haematologic tests (CBC, Blood

Smear, Total Lymphocyte Count) and immunologic tests (IgG, IgM, IgA, C3-C4) and heparinised blood for lymphocyte subgroups (CD3-CD4) were drawn.

Immunoglobulins and complements were measured by Radial Immunodiffusion (Kallested Lab. Chaska, USA) method while lymphocyte subgroups were evaluated by means of anti-clonal antibodies (Sero-tek anti-human antibodies, England) and of Olympus PM 10 AD immunofluorescent microscope (13,14).

All data is were analysed by paired and intergroup unpaired tests. Significance level is accepted as $p < 0,05$.

Results

The 2 groups were similar for ages, weights and anaesthesia-periods ($p > 0,05$) (Table 1).

Table 1. Demographic characteristics of the patients

	1. group (Propofol)	2. group (Thiopentone)
n	20	20
Sex (F/M)	10/10	14/6
Age (Year)	38.4±11.4	39.5±8.82
Weigh (kg)	72.9±12.9	71.5±14.7
Time of anesthesia (min)	84.5±22.65	76.0±21.74

* $p > 0,05$ (There is no statistical difference between two groups).

Postoperativur 30 th minute IgM, IgA, IgG and C3 concentrations were significantly different than of preoperative consanstransions in the group propofol applied by TIVA but C4 consanstransions of pre-op and postoperativur periods were not significantly different (Table 2).

In the thiopentone applied group decreasing in IgM, IgA, C4 consanstransions were significant while decreasing in IgG and C3 consanstransions were insignificant (Table 3). When a comparison was made between the consanstrations at postoperativur 30th minute and 24 th hour in the first group, increase in serum IgM, IgG and C3 and decrease in serum IgA were statistically significant ($p < 0,05$) while there were no significance for changes of IgG and C4 consanstrations ($p > 0,05$) (Table 2). On the other hand, the consanstrations in the thiopentone applied group there was no significant increasing in IgG, IgM, IgA, C3, C4 ($p > 0,05$) (Table 3).

Table 2. Mean serum IgG, M, A and C3 -C4 concentrations at pre-op 30 th , postoperativur 30 th minute and postoperativur 24 th hour in the case of using propofol

	Pre-op	Postoperativur 30 th Min.	Postoperativur 24th hours
IgG	1625±356.7(*)	1247.5±414.7	1355.0±527.0
IgM	160.75±19.62(*)	138.25±39.5(***)	176.5±61.3
IgA	187.9±93.1(*)(**)	136.8±49.5(***)	116.5±45.1
C3	153.85±33.18(*)	139.15±28.5(***)	149.5±29.46
C4	39.3±9.15	37.55±13.68	41.35±15.74

* p<0.05 at pre-op and postoperativur 30 th minutes.

** p<0.05 at pre-op and postoperativur 24 th hours.

*** p<0.05 at postoperativur 30 th minutes and postoperativur 24 th hours.

When immunoglobulin and compleman concentrations of the both groups were matched, there was a significant decrease in IgG concentrations at both pre-op and postoperativur 30 th minutes and in IgA concentrations at postoperativur 30th minute and 24th hour in the propofol applied group (p<0,05).

When CD4, CD8, leucocyte and lymphocyte values were compared between the both groups, there was a significant decreasing in leucocyte and lymphocyte numbers of that group in which propofol applied (p>0,05) while a significant change was not found in CD4 and CD8 values of Table 3. Mean serum IgG, M, A and C3 -C4 values at pre-op 30th, postoperativur 30th minute and postoperativur 24 th hour in the case of using the thiopentol

the both groups (p>0,05)(Table 4). Decreasing in CD4, leucocyte and lymphocyte values of the propofol applied group was significant whereas of the other group was insignificant (p<0,05) (Table 5). Values at postoperativur 30 th minute and 24 th hour in the both groups were also insignificant (p>0,05) (Table 5). The PPD test was applied on all patients. A significance was found between pre-op (2 days before) and postoperativur (2 days later) endurance diameters (p<0,05) where as there was no significance between the both groups (p>0,05).

	Pre-op	Postoperativur 30th Min.	Postoperativur 24th Hours
IgG	1108.0±461	1050.0±406.2	1062.0±592
IgM	212.0±119.5(*)	186.5±87.3	196.5±110.2
IgA	235.7±109(*)(**)	143.8±49.1	152.5±72.2
C3	120.9±31.53	113.75±24.43	120.75±29.35
C4	29.9±9.56(*)	26.2±10.04	27.25±12.77

* p<0.05 at pre-op and postoperativur 30th Min.

** p<0.05 at preop and postoperativur 24th hours.

Table 4. Mean CD3-CD4 leucocyte and lymphocyte numbers at pre-op 30th, postoperativur 30 th minutes and postoperativur 24 th hour in the case of using propofol

	Pre-op	Postoperativur 30th Min.	Postoperativur 24th Hours
CD4	40.8±6.07(**)	43.15±11.6(***)	50.25±8.99
CD8	53.55±7.29(*)	45.95±5.31(***)	49.25±1.92
Leucocyte	11435±3136(*)(**)	9653±3263	9500±3089
Lymphocyte	61.5±5.3(*)(**)	54.65±6.67(***)	58.95±4.05

* p<0.05 at pre-op and postoperativur 30th Min.

** p<0.05 at pre-op and postoperativur 24th hours.

*** p<0.05 at postoperativur 30th Min. and postoperativur 24th hours.

Table 5. Mean CD3-CD4 leucocyte and lymphocyte numbers at pre-op 30th, postoperativer 30 th minutes and postoperativer 24 th hour in the case of using thiopentone

	Pre-op	Postoperativer 30th Min.	Postoperativer 24th hours
CD4	39.35 ± 4.0	36.8 ± 7.9	40.15 ± 5.98
CD8	44.5 ± 8.89(*)	41.2 ± 7.42	44.8 ± 6.17
Leucocyte	7365 ± 3271(*)(**)	6760 ± 2589	6720 ± 2592
Lymphocyte	58.4 ± 5.09(*)	56.1 ± 5.52(***)	58.05 ± 4.24

* p < 0.05 at pre-op and postoperativer 30th Min.

** p < 0.05 at pre-op and postoperativer 24th hours.

*** p < 0.05 at postoperativer 30th Min. and postoperativer 24th hours.

Discussion

Although anaesthetic agents have usually an inhibitory effect on bacterial growth (5), they may depress directly or/and indirectly the immune system by means of hormones thus may increase infection risk, may depress healing or may facilitate spreading of malign disorders(5,15).

One must analyse the immunoglobulins and complement system, which are variables of the immune system, in order to determine effects of anaesthetic agents on humoral immune system.

Propofol's effect on humoral immune system was compared with of isoflurane in a study(16), and reported that IgA and IgM concentrations had decreased, IgG concentrations had increased in isoflurane applied cases at 4th day whereas IgM and IgA concentrations had decreased and there had been no change in IgG concentrations. In another study by Erol *et al* (17) to reveal for revealing effects of propofol anaesthesia on the humoral immune systems, they applied the anaesthetic agent at a dose of 2 mg/kg for induction and 7 mg/kg for maintenance on 23 adults and measured immunoglobulin and complement concentrations before and after anaesthesia and 4 days later by the turbidometry method. They found significant decreasing in IgG, IgM, IgA and C4 in the postoperativer period and in IgG and IgM concentrations at the postoperativer 4th day, and also significant increase in C3, C4 at the postoperativer 4th day.

Doenicke *et al* (18) applied 2 mg/kg propofol for induction on 32 volunteer healthy adults, made waken them without exposing any operation then measured their serum immunoglobulin and complement concentrations by laser nephelometry and racist immunoelectrophoresis respectively, before anaesthesia and 1 day later, and did not found a significant change. These contra-

dicting results of the 2 researches may be due to differences in methods, and, as in Doenicke, having no surgical operation and applying low-dose propofol. We found that there was a significant decrease in IgG, M and A concentrations at postoperativer 30th minute, and in IgA concentrations at postoperativer 24th hour in the propofol applied group by TIVA. Decreasing of IgA at postoperativer 30 minute may be due to hemodilution but decreasing of IgA, at postoperativer 24th hour is due to anesthetic agent. Other immunoglobulin concentrations begun increasing towards 24th hour due to disappearing of the dilutional effect. This also may be due to patients to began oral taking, neurohumoral changes developed by stress reaction to turn back normal and hemodilutional effect to go away gradually. Lasting of decreasing IgA concentrations until the 24th hour is contrary to the other studies. We found IgM and IgA to be decreased and IgG to be unchanged in the Thiopentone applied group. Unchanging concentrations of IgG, a pillar of humoral immune system, indicates unimportance of the immunosuppression caused by anesthetic agents.

Decrease in IgA, and IgM were in harmony with some studies in which halothane, enflurane spiral anaesthesia, neurolept anaesthesia, acupuncture or fentanyl by transcutan stimulation had been applied, but unchanging of IgG was contrary to their results (16,19,20,21). Thiopentone had a smaller effect than propofol on the complement system while decreasing in C4 level at postoperativer 30th minute was an unexpected one in our study.

A decrease in IgA leads local infections whereas a decreased IgM delays primary immune response. Most important duty in immune response is of IgG. For that reason its supposed that thiopentone does not effect the immunity

very much although it may increase risk for infection. Tough propofol may increase risk for infection and interfere with body defence system, it does not effect local immunity leading ineffective immune response. Main function of the complement system is related to the humoral immunity. The system also play an important role in host defence by regulating the leucocyte migration and easing the lysosomes to come out from the phagocytes. Therefore decrease in their serum consantrations may not be throughly correlated with those of immunoglobulins. However serum compleman consantrations increase in the event of an increase in any case of increasing humoral immunresponse.

Erol et al.(17) reported that C4 consantrations had decreased after operation whereas C3 and C4 consantrations had significantly increased at postoperatuvur 4th day. In another study(16) it was found that decrease in C3 and C4 consantrations in isofluran applied cases and decrease just in C4 in propofol applied cases at postoperatuvur 30th minute were considerable whereas increasing of C3 and C4 consantrations in both propofol and isofluran applied cases at postoperatuvur 4 th day were significant. Doenicke et al. observed no significant variation in complement consan-transions in their study(18).

At postoperatuvur 30th minute, decreasing of C4 consantrations in the thiopentone applied group and of C3 consantrations in the propofol applied group were observed in our study, it's also observed that there was a significant increasing of C3 in the propofol applied cases at 24th hour. Increasing of C3, which has anaphylo toxic and chemotoxic activities suggests humoral and cellular immunresponse activation.

It's reported that, after researching by the PHA method, both propofol and thiopentone had positive effect on activation of the T cells, B cells, CD4 and CD8. Propofol had more effect on the CD4 activation (15) NK activity in that study reported to be decreased. Decrease in CD4 activity is in harmony with that one reported by Pirttikangas et al where as increase in CD8 activity is contrary to that (22).

Observation of no significant change except decreasing of CD4 in the thiopentone applied group is similar to the findings by Salo et al.(20). To reveal thiopentone's effect on the immunosystem in general and on the spinal anaesthesia, changes in the T, Th, Ts, NK cells, IgG, IgM and IgA consantrations were measured and no significant variation was observed(20).

Relative decrease in leucocyte and lymphocyte counts and unsignificance of the difference between both groups may be depend on hemodilution. Enduration diameters of the PPD significantly decreased after anaesthesia and operation. This was more prominent in the propofol applied group and in hamony with the other variations in cellular and humoral immunity parameters.

In conclusion we compared effects of propofol and thiopentone on the immune system at humoral and cellular points and found propofol to have greater effect. This may depend on directly chemical structure of the propofol (soya bean oil, egg-phospholipid and gliserol) or indirectly cytokines mediated by the agents. Although the propofol has a less toxic effect relative to other anaesthetics in immunodepressive patients.

It's immunosuppressive in vitro because of its lipid gradient at higher concentrations(23,24). On the other hand when compared with the thiopentone the propofol has a more increasing effect on TNF-alpha and IL-1 alpha synthesis, and a more decreasing effect on IL-1B and th-2 synthesis while has no effect on IL-6, TNF synthesis(18,25,26). We suggest that on must be carefull while choosing patients for the propofol anaesthesia because of its considerable immunosuppressive effect. So it's wise full not to use propofol as anesthetic in cases in which immunosuppression may be risky, i.e. those taking immunosuppressive drugs and -if it's used- patients must be properly protected against the infection risk in the short term postoperatuvur period.

References

1. Serniğil S., Gürel N., Özkan T., Pembeci K., Akbir K.: Halotane, Enfluran ve Rejyonal anestezi uygulaması sonucunda lenosit alt gruplarında ortaya çıkan değişiklikler, *Nevşehir XXIII. Türk Anest. ve Rean. Kongresi Özet Kitabı*, 7, 1993.
2. Dökken JG.: *Immunoloji*, İstanbul, Sandoz Yayınları, 5-30, 1992.
3. Elaz Z.: *Anestezi el kitabı*, İzmir: Güven Kitabevi, 10-5, 1982.
4. Erençil A.: *Anestezi ve monitörasyon*, İstanbul: İkinci Basılı, Nobel, 1992.
5. Esener Z.: *Klinik Anestezi*, Samsun: Logos Yayıncılık, 1991:167-9, 1991.
6. Kaşaplı SO.: *Tıbbi İmmunoloji*, Ankara: Feyal Matbaacılık, 1704 - 56, 1993.
7. Sun S.: *İntravenöz anesteziye son gelişmeler ve propofol*, *Türk Anest. ve Rean. Cem. Mecm.* 17 (S1):197-198, 1989.
8. Sun S., Kose Y., Özkoca S.: *Propofol ve indüksiyon*, *Türk Anest. ve Rean. Cem. Mecm.* 17 (S1): 202-205, 1989.

9. Karobiyik L., Bozkarlı F., Çelebi H.: Propofol-alfentanil ile TIVA Genel anestezi ile hemodinamik ve derlenme özellikleri açısından karşılaştırılması, Nevşehir XXIV Türk Anest. ve Rean. Kongresi Kitabı, 87, 1993.
10. Rupprecht J., Dorojic M., Kesercioğlu J.: Recovery from propofol-TIVA, Nevşehir XXIV Türk Anest. ve Rean. Kongresi Kitabı, 43, 1993.
11. Bozkarlı F., Ersoy S., Çelebi H., Karobiyik L.: Propofol ve thiopentolün hissinin salınımına etkilerinin karşılaştırılması, Türk Anest. ve Rean. Cem. Mecm., 20: 172-174, 1992.
12. Yuvacıoğlu B., Tokat O., Özcan B., Kılıncı F.: Thiopentol, propofol ve etomidatın anestezisi indüksiyonu ve endotelenül antitübasyon sırasında hemodinamik etkilerinin karşılaştırılması, 20: 284-287, 1992.
13. Bülgeci H.: Klinik Mikrobiyoloji Tanı, 1.bast, Birej Kitabevi, 1992.
14. Bolcalı AK: Deneysel Parazitik Enfeksiyonlarda Serum Çinko Düzeyleri ve Çinko Talaklarının Hücreli Bağışıklığı Etkisi, Konya Doktora Tezi, 1993.
15. Marcus V., Payne J.: The induction of anesthesia with propofol compared in normal and renal failure patients, Postgrad. Med. J. 61: 62-63, 1985.
16. Erol U., Özgöven V., Ayar Ü.: İsofluran ve propofol anestezisinin serum IgA, IgM, IgG, C3, C4 düzeylerine olan etkileri, Türk Anest. ve Rean. Cem. Mecm., 21:297-302, 1992.
17. Erol U., Özgöven V., Çelebioğlu B., Ayar Ü.: Propofol ve hümonal immünte, Türk Anest. ve Rean. Cem. Mecm., 20: 261-264, 1992.
18. Dowdke A., Lorenz W., Starworth D., Doka T., Glen JB.: Effect of propofol on histamine release, immunoglobulin levels and activation of complement in healthy volunteers, Postgraduated Med. J. 61(53): 15-20, 1985.
19. Bayhan N., Günelkermi M., Pili, G.: "Sectio" sezaryen operasyonlarında indüksiyon ve idamede thiopentone ile propofolun karşılaştırılması, Türk Anest. ve Rean. Cem. Mecm., 20: 300-304, 1992.
20. Selo M., Nissila M.: Cell-mediated and humoral immune responses to total hip replacement under spinal and general anaesthesia, Acta Anaesthesiol. Scand. 34: 241-248, 1990.
21. Spas V., Botvinkov N., Adonkin F.: The effect of analgesia on immunoglobulin blood level, Act. Anest. 1: 617, 1987.
22. Pitirikkangas CO., Penttilä J., Selo M., Veimo O.: Effects of propofol infusion anaesthesia on immune functions in minor surgery, Acta Anest. Scand. 37:236, 1993.
23. Esmaoğlu A., Boyacı A., Sofuoğlu S.: Elektrokuvüsil tedavide anestezik ajan olarak propofol ve thiopentone karşılaştırılması, Türk Anest. ve Rean. Cem. Mecm. 21: 289-292, 1993.
24. Varagnoli BM.: Experience of propofol anaesthesia for use in tumour pathology, Review for Medical and Pharmacological Sciences, 14: 143-145, 1992.
25. Boudash N., Laon M.: Effect of intravenous anaesthetic agents on cytokine production in cultured peripheral blood mononuclear cells, Anaesthesiology, 79: 711, 1993.
26. Rosen D., Couder D., Ramsbacher L.: An anaesthetic induced platelet dysfunction between flthane, ethreine and isoflorsene, Anest. Analg. 67: 266, 1988.

Correspondence to:

Mustafa ALTINDIŞ

Selçuk Üniversitesi Tıp Fakültesi,

Mikrobiyoloji ve Klinik Mikrobiyoloji ABD

42080 Konya

Tel - Fax : (332) 323 26 41